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**Genetic associations between cognitive ability, negative
emotions, and mental and physical health**

Saskia P. Hagenaars



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Dedicated to Stef and Wies

Abstract

Human population-based studies have shown that cognitive ability and negative emotions are associated with later health outcomes. Part of this association might be due to shared genetic influences. The present thesis has two main objectives. The first is to examine the shared genetic aetiology between cognitive ability and mental and physical health. The second is to examine the shared genetic aetiology between the tendency to experience negative emotions and mental and physical health.

Chapter 1 and Chapter 2 provide an introductory overview of the field of individual differences in psychology, with the first Chapter focussing on cognitive ability and the second on personality (especially neuroticism). Each of these Chapters provide an historical overview of the two traits, followed by the associations with health outcomes, and finish by exploring the genetic aetiology of both cognitive ability and negative emotions and the potential genetic overlap with health outcomes.

Chapter 3 focusses on the main cohort analysed in this thesis, the UK Biobank. This Chapter outlines the study population and its demographics, and provides a detailed account of the main variables examined in this thesis.

Chapters 4 to 7 present the empirical work and are split in two parts; the first part (Chapters 4 and 5), focusses on cognitive ability. The second part (Chapters 6 and 7) focusses on negative emotions.

Chapter 4 presents two studies, examining the shared genetic aetiology between cognitive ability and mental and physical health using linkage disequilibrium score regression and polygenic profile analysis; Mendelian Randomization is used to test for direction of effect between cognitive ability and physical health. The results indicate a substantially shared genetic aetiology between cognitive ability and both physical and mental health. No evidence was found for a causal association between cognitive ability and physical health.

Chapter 5 examines the genetic aetiology of a test of executive cognitive function, the Trail-Making test, which has been closely associated with other cognitive abilities. This Chapter also examines the shared genetic aetiology between the Trail-Making test, general cognitive ability, processing speed, and memory, using a range of molecular genetic techniques. The results provide heritability estimates ranging from 7% to 22% for the different Trail-Making test measures, and there are new genetic associations with the Trail-Making test. A considerable degree of genetic overlap is found between the Trail-Making test and general cognitive function and processing speed in particular.

Chapter 6 explores the shared genetic aetiology between the personality trait of neuroticism and mental and physical health using Linkage Disequilibrium Score Regression and polygenic profile analysis. The results show significant genetic correlations between neuroticism and major depressive disorder, schizophrenia, and anorexia. Polygenic profile scores for multiple mental health traits, as well as body mass index, coronary artery disease, and smoking status are predictive of neuroticism.

Chapter 7 examines the genetic contributions to self-reported tiredness, a trait strongly related to the tendency to experience negative emotions; it also examines the genetic overlap with health outcomes using Linkage Disequilibrium Score Regression and polygenic profile analysis. The results demonstrate a significant heritability estimate of 8% for self-reported tiredness. Extensive genetic overlap is identified between self-reported tiredness and mental and physical health, and particularly with the trait of neuroticism.

Finally, Chapter 8 summarizes the empirical findings presented in Chapters 4 to 7. This Chapter discusses limitations of the methods used in this thesis, and offers suggestions for future research in the field of genetic epidemiology, especially as applied to health and psychological differences.

Lay summary

Some studies have shown that how effectively people think and how they experience negative emotions is linked with how healthy they are in later life. People's thinking skills – referred to as cognitive ability, negative emotions, and health are all partly influenced by genes. It is therefore possible that the association between cognitive ability, negative emotions, and health is partly due to genetic influences. This Thesis will be split in two parts to address the possibility of genetic influences on the relation between cognitive ability and health in the first part, and between negative emotions and health in the second part. The first study in this Thesis showed that genes associated with different health outcomes were also associated with various tests of cognitive ability, which supports the idea that better overall health is likely linked to higher levels of intelligence. We did not find evidence for a causal link between cognitive ability and physical health in any direction. The following study in the cognitive ability part of this Thesis examined the genetic background of the Trail Making Test, a measure of mental flexibility, and we showed that genes for this test were also genes that are involved in other measures of cognitive ability.

In the second part of the thesis we found that genes for the personality trait of neuroticism, which is the tendency to experience negative emotions, are also genes linked to mental health diseases. Healthy individuals with more genes for mental health diseases and physical health outcomes had higher scores for neuroticism. A second study in this part of the Thesis used a measure related to negative emotions, which was self-reported tiredness, and found that genetics account for about eight percent of people's differences in self-reported tiredness; which implies that the vast majority of people's differences in self-reported tiredness are environmental in origin. We found that the small genetic contributions to self-reported tiredness overlapped with genetic contributions to multiple mental and physical health conditions. Overall, the results in this Thesis provide further evidence for genetic links between cognitive ability and health, and between negative emotions and health.

Declaration

I declare that the thesis has been composed by myself and that the work has not been submitted for any other degree or professional qualification. I confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

The work presented in Section 4.2 was previously published in *Molecular Psychiatry* as “Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112 151) and 24 GWAS consortia” by SP Hagenaars (student), SE Harris (supervisor), G Davies, WD Hill, DCM Liewald, SJ Ritchie, RE Marioni, C Fawns-Ritchie, B Cullen, R Malik, METASTROKE Consortium, International Consortium for Blood Pressure GWAS, SpiroMeta Consortium, CHARGE Consortium Pulmonary Group, CHARGE Consortium Aging and Longevity Group, BB Worrall, CLM Sudlow, JM Wardlaw, J Gallacher, J Pell, AM McIntosh (supervisor), DJ Smith, CR Gale, and IJ Deary (supervisor). This study was conceived by all authors. Author contributions (student’s contributions in bold): conceived and designed experiments: IJD CRG. Data curation: **SPH** SEH GD REM DCML CRG. Performed the experiments: polygenic profile analysis: **SPH**, genetic correlations: WDH. Wrote draft: introduction: IJD CRG SJR, methods: **SPH** SEH, results: **SPH** IJD, discussion: **SPH** IJD SEH WDH CRG. Figures and tables: **SPH**. Reviewed draft: **all authors**. **SPH** and SEH contributed equally to this study, CRG and IJD contributed equally to this study.

The work presented in Section 4.3 was previously submitted to *Scientific Reports* as “Cognitive ability and physical health: a Mendelian randomization study” by SP Hagenaars

(student), SE Harris (supervisor), CR Gale, and IJ Deary (supervisor). This study was conceived by all authors. Author contributions (student's contributions in bold): conceived and designed experiments: **SPH** SEH. Data curation: **SPH** SEH CRG. Performed the experiments: **SPH**. Wrote draft: introduction: **SPH** SEH, methods: **SPH**, results: **SPH**, discussion: **SPH** SEH. Figures and tables: **SPH**. Reviewed draft: **all authors**.

The work presented in Chapter 5 was previously submitted to *Molecular Psychiatry* as “Genetic contributions to trail making test performance in UK Biobank” by SP Hagenaaars (student), SR Cox, WD Hill, G Davies, DCM Liewald, CHARGE consortium Cognitive Working Group, SE Harris (supervisor), AM McIntosh (supervisor), CR Gale, IJ Deary (supervisor). This study was conceived by all authors. Author contributions (student's contributions in bold): conceived and designed experiments: **SPH** GD IJD. Data curation: **SPH** SEH GD DCML CRG. Performed the experiments: **SPH** (phenotypic associations, genome-wide association analysis, SNP based heritability, genetic correlations, gene-based associations CHARGE consortium measures, polygenic prediction, meta-analysis), WDH (gene-based association analysis UK Biobank measures, partitioned heritability). Wrote draft: introduction: **SPH** SRC, methods: **SPH**, results: **SPH**, discussion: **SPH**. Figures and tables: **SPH**. Reviewed draft: **all authors**. CRG and IJD contributed equally to this study.

The work presented in Chapter 6 was previously published in *Translational Psychiatry* as “Pleiotropy between neuroticism and physical and mental health: findings from 108 038 men and women in UK Biobank” by CR Gale, SP Hagenaaars (student), G Davies, WD Hill, DCM Liewald, B Cullen, BW Penninx, International Consortium for Blood Pressure GWAS, CHARGE Consortium Aging and Longevity Group, DI Boomsma, J Pell, AM McIntosh (supervisor), DJ Smith, IJ Deary (supervisor), and SE Harris (supervisor). This study was conceived by all authors. Author contributions (student's contributions in bold): conceived and designed experiments: CRG IJD. Data curation: **SPH** SEH GD DCML CRG. Performed

the experiments: **SPH**. Wrote draft: introduction: CRG, methods: CRG **SPH**, results: **SPH**, discussion: CRG **SPH** IJD SEH. Figures and tables: **SPH**. Reviewed draft: **all authors**. CRG and **SPH** contributed equally to this study. IJD and SEH contributed equally to this study.

The work presented in Chapter 7 was previously published in *Molecular Psychiatry* as “Genetic contributions to self-reported tiredness” by V Deary, SP Hagenaars (student), SE Harris (supervisor), WD Hill, G Davies, DCM Liewald, International Consortium for Blood Pressure GWAS, CHARGE Consortium Aging and Longevity Group, CHARGE Consortium Inflammation Group, AM McIntosh (supervisor), CR Gale, and IJ Deary (supervisor). This study was conceived by all authors. Author contributions (student’s contributions in bold): conceived and designed experiments: VD **SPH** IJD. Data curation: **SPH** SEH GD DCML CRG. Performed the experiments: **SPH** (phenotypic associations, genome-wide association study, SNP-based heritability, genetic correlations, polygenic prediction analysis, age- and sex- stratified analysis), WDH (partitioned heritability, gene-based association analysis). Wrote draft: introduction: VD **SPH** IJD, methods: **SPH**, results: **SPH**, discussion: VD **SPH** IJD. Figures and tables: **SPH**. Reviewed draft: **all authors**. VD and **SPH** contributed equally to this study. CRG and IJD contributed equally to this study.

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To acknowledge the contributions of many co-authors, “we” will be used instead of “I” throughout the Chapters of this Thesis.

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1. Cognitive ability

The field of differential psychology is a well-established part of psychological science and studies how people differ from each other, as well as the potential implications of those differences. While this discipline does not have clear boundaries regarding its subject, the term ‘individual differences’ is generally used to refer to the traits of cognitive ability and personality. Research in the past century has led to the development of multiple theories of cognitive ability (intelligence) and personality, explanations of what causes differences in both traits, and the impact of those differences for example on health outcomes. Evidence in the field of individual differences has related both cognitive ability and personality to health outcomes (I. J. Deary, Weiss, & Batty, 2010; Lahey, 2009; Watson & Pennebaker, 1989; Wraw, Deary, Der, & Gale, 2016; Wraw, Deary, Gale, & Der, 2015). These findings have implications for psychologists, epidemiologists, clinicians, and policy makers by providing further evidence of the predictive validity of both cognitive ability and personality, as well as contributing to the understanding of health inequalities in the population. This Chapter and Chapter 2 will present the latest evidence on the phenotypic and genetic associations of cognitive ability and personality with health outcomes. Here, cognitive ability (Chapter 1) and personality (Chapter 2), in particular negative emotions, will be examined separately. Firstly, a brief historical context of the trait will be outlined. Secondly, evidence from the field’s empirical work will be presented on the association between cognitive ability or negative emotions and health, bringing together both psychology and epidemiology. Finally, empirical work on the possible shared genetic aetiology of cognitive ability, negative emotions and health, with attention to the methods used to examine a genetic aetiology, will be presented.

1.1. History of cognitive ability

Ever since the Classical Greek times, cognitive ability (also named intelligence) has been recognised as one of the most important individual differences. Plato distinguished three elements of the human soul; intellect, emotion, and will. He compared intellect to the thinking part of the soul. Aristotle then combined the emotion and will elements to 'oretic' capacities. Finally, Cicero translated the intellectual components of the human soul based on Plato and Aristotle to 'intelligentia' (H. J. Eysenck, 1979).

Testing differences in intelligence started to take place in the mid-to-late nineteenth century, with Sir Francis Galton being one of the pioneers in this area (Galton, 1869). Galton, Charles Darwin's half cousin, believed that the natural selection theory could also be applied to human intelligence. He collected data on about 10,000 individuals who visited the 'Anthropometric Laboratory' at the International Health Exhibition in South Kensington, London, including data on several physical measures, reaction times to visual and auditory stimuli, and social class (Galton, 1885; Johnson et al., 1985), aiming to measure individual differences in cognitive abilities.

1.1.1. Spearman's construct of general intelligence

Many theories of intelligence have been developed and the two most common ones are Charles Spearman's construct of 'general intelligence' and Horn and Cattell's theory of fluid and crystallized intelligence (Section 1.1.2). In 1904, Charles Spearman (1863 – 1945) proposed the construct of 'general intelligence', when he was examining the results of children's school exams as well as teacher's ratings of cognitive ability (Spearman, 1904). Intelligence tests generally consist of multiple subdomains, each testing a different cognitive ability. He found that both the scores on the different examinations, and teacher's ratings of cognitive abilities, were highly correlated. He concluded that the correlations between the variables could be best

explained by a single latent or unobserved factor underlying performance in all of the ability measures. Spearman's theory originally consisted of two factors; one general factor that every cognitive task requires (*g*), as well as skills specific to each cognitive task that are not shared between each other (*s*) (Figure 1-1). Over time, relatively greater importance has been placed on the general factor of intelligence (Spearman, 1927). Spearman's theory of intelligence has been criticized numerous times, but till this day it is still one of the most used constructs in intelligence research (Carroll, 1993).

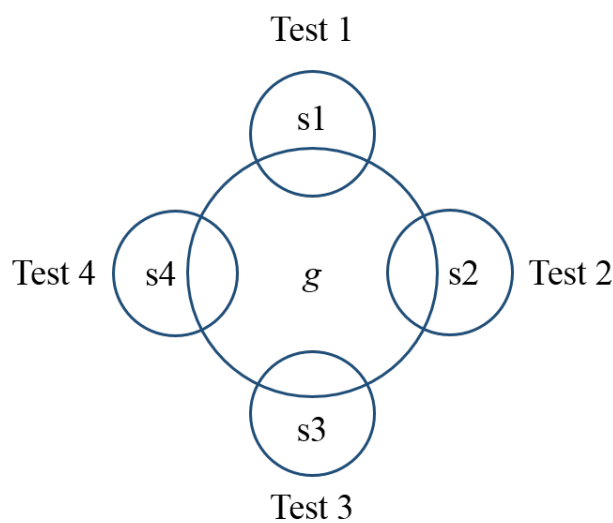


Figure 1-1. Spearman's two factor theory; all cognitive abilities have an area of overlap (*g*), but each ability also depends on specific factors (*s*).

1.1.2. Horn and Cattell's theory of fluid and crystallized intelligence

Raymond Cattell first proposed that intelligence is not a unitary construct, but assumes two broad types of intelligence, which he named fluid (*Gf*) and crystallized (*Gc*) intelligence (Cattell, 1940, 1943b). His student John Horn, further developed this construct (Horn & Cattell, 1966). *Gf* represents the ability to perform well on non-verbal tasks that involve reasoning, working memory, and processing speed, while *Gc* represents the ability to do well on verbal tasks which involve knowledge and abilities acquired via experience. Many cognitive domains, in particular domains related to *Gf*, show an age-related decline over time,

and this is frequently referred to as healthy cognitive ageing. There is, however, great widespread variation in the onset and rate of this so called ‘cognitive ageing’ (Hedden & Gabrieli, 2004; Salthouse, 2009). As shown in Figure 1-2, the measures displaying an age-related decline, involve Gf and measures that are part of Gf. Gc displays an increase up to age 60 and declines thereafter.

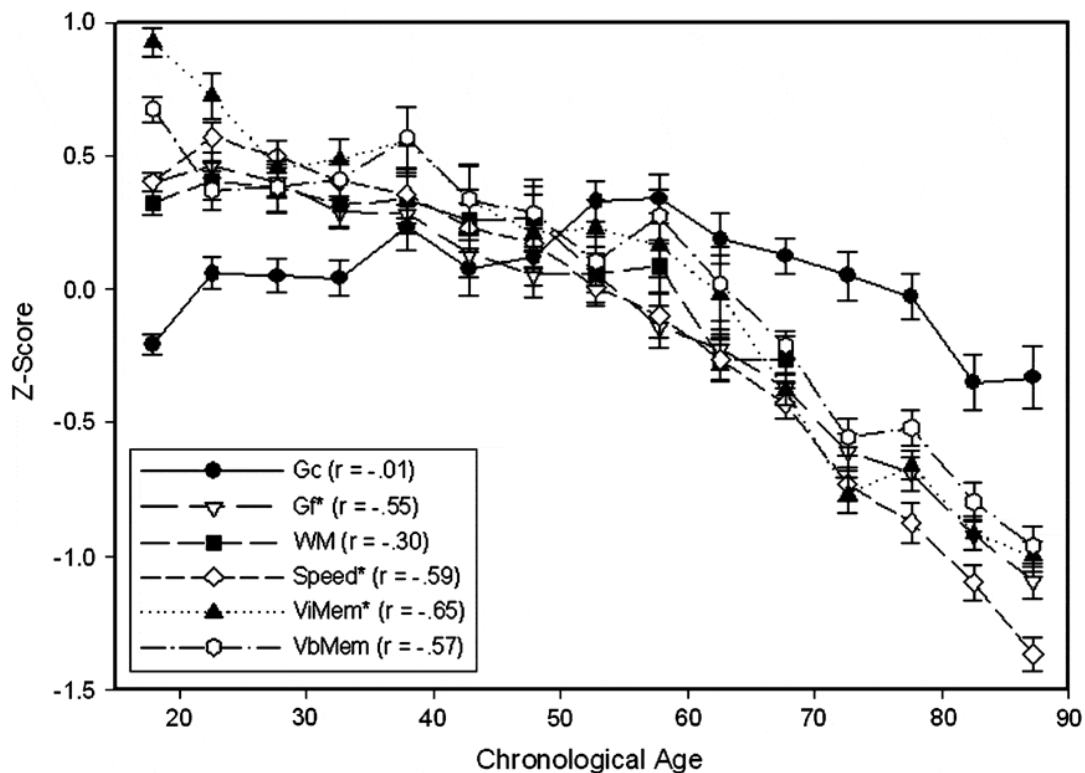


Figure 1-2. Age relations on composite cognitive scores. These are formed by averaging the z-scores for the variables contributing to each factor. Gc, crystallized cognitive ability; Gf, fluid cognitive ability; WM, working memory; ViMem, visual memory; VbMem, verbal memory. Reprinted with permission from Salthouse (2009). Copyright 2009 by Cambridge University Press.

The theory of fluid and crystallized intelligence is widely accepted among psychologists and to quote John Carroll it “appears to offer the most well founded and reasonable approach to an acceptable theory of the structure of cognitive abilities” (Carroll, 1993, p. 62). However, the theory of fluid and crystallized intelligence does not provide a third order factor to account for

the correlations between fluid and crystallized intelligence, which has been addressed by John Carroll, as discussed in Section 1.1.3.

1.1.3. Carroll's three-stratum model

In a further attempt to resolve the phenotypic structure of human cognitive abilities, John Carroll proposed the three-stratum model of intelligence (Carroll, 1993). According to Carroll the fluid and crystallized model by Cattell and Horn did not accept a general factor of intelligence as an explanation for the correlations between the fluid and crystallized abilities. He based his model on the analyses of more than 460 sets of intelligence test scores. His three-stratum model supports the positive manifold of correlations between intelligence domains, acknowledging the general factor of intelligence. Carroll's model includes three strata with in the third stratum a general factor of intelligence, multiple broad abilities in the second stratum and many specific or narrow abilities in the first stratum (Figure 1-3). The second stratum is very similar to the abilities of the crystallized and fluid abilities in the Horn and Cattell model, but also includes memory, visual and auditory perception, retrieval ability, cognitive speed and processing speed. Other models might include abilities such as processing speed as part of fluid cognitive ability. The narrow abilities in the first stratum are based on specific cognitive tests.

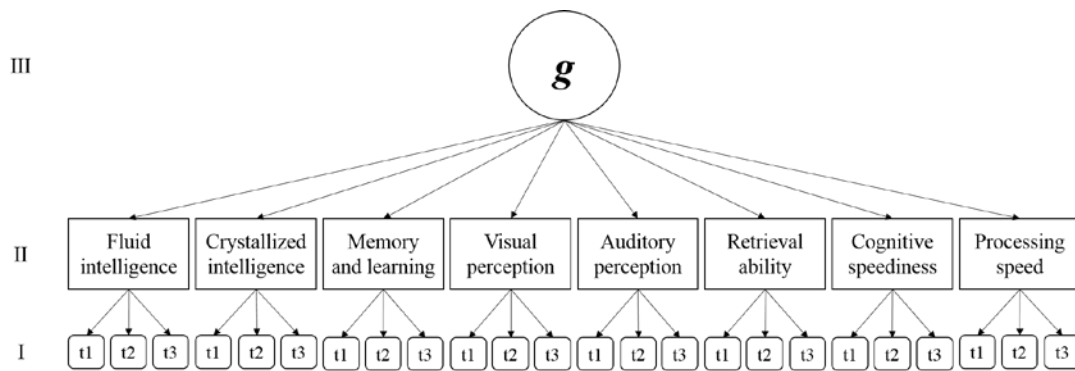


Figure 1-3. The structure of human cognitive abilities according to the three-stratum model. Adapted with permission from Carroll (1993). Copyright 1993 by Cambridge University Press.

1.2. Cognitive epidemiology

Cognitive epidemiology is part of the field of individual differences that seeks to understand the associations between cognitive ability and health (I. J. Deary, 2010; I. J. Deary & Batty, 2007; I. J. Deary et al., 2010). In general, cognitive epidemiology has been particularly concerned with childhood ability and its association with health in later life. In the late 1980s the first peer reviewed studies examining the association between intelligence and mortality appeared (O'Toole, Adena, & Jones, 1988; O'Toole & Stankov, 1992). O'Toole et al. (1988) found that in Australian servicemen those with lower scores on the army intelligence test had higher risks of mortality. Participation in post-secondary education was associated with lower risk of early death and was more important than years of education or degree attainment, which indicated that participation itself rather than the time spend in education is important in the association between education and mortality (O'Toole et al., 1988). The first study to examine the association between childhood cognitive ability and all-cause mortality was a longitudinal population-wide study including 80% (N = 2230) of children born in Aberdeen in 1921, as part of the Scottish Mental Survey 1932, with a follow-up time of 65 years (Whalley & Deary, 2001). The results showed that one SD increase in childhood cognitive ability was associated with a hazard ratio of 0.79 (95% CI 0.75 to 0.84) for mortality risk at age 76 years. This study

brought the association between childhood cognitive ability and mortality a wider readership, leading the area of individual differences into the field of public health.

1.2.1. Mortality

Many cognitive epidemiology studies examine the association between cognitive ability and mortality. A large cohort study of just under 1 million Swedish men found a stepwise negative association between intelligence and mortality, each one-point decrease on a nine-point intelligence scale was associated with an increase in mortality rate (HR = 1.15, 95% CI = 1.14 – 1.16) (Batty et al., 2009), as shown in Figure 1-4. This association remained the same when correcting for physical measures (height, BMI, and blood pressure) or parental social class, but did decrease when educational attainment was controlled for. One could argue that it is not appropriate to control for educational attainment in studies of cognitive ability, as recent studies have shown educational attainment to be a good proxy measure for cognitive ability (I. J. Deary & Johnson, 2010; Hill, Davies, Liewald, McIntosh, & Deary, 2016; Rietveld et al., 2014). Similar findings between cognitive ability and mortality were found in a large meta-analysis that also included the Batty et al. (2009) study, where one SD increase in childhood intelligence was associated with a 24% lower mortality risk (HR = 0.76, 95% CI = 0.75 – 0.77) (Calvin et al., 2011). A cohort study including 728,160 men from the Danish Conscription Database, showed a 28% higher risk of dying for all-cause mortality for each SD decrease in cognitive ability (HR = 1.28, 95% CI = 1.27 – 1.29) (G. T. Christensen, Mortensen, Christensen, & Osler, 2016).

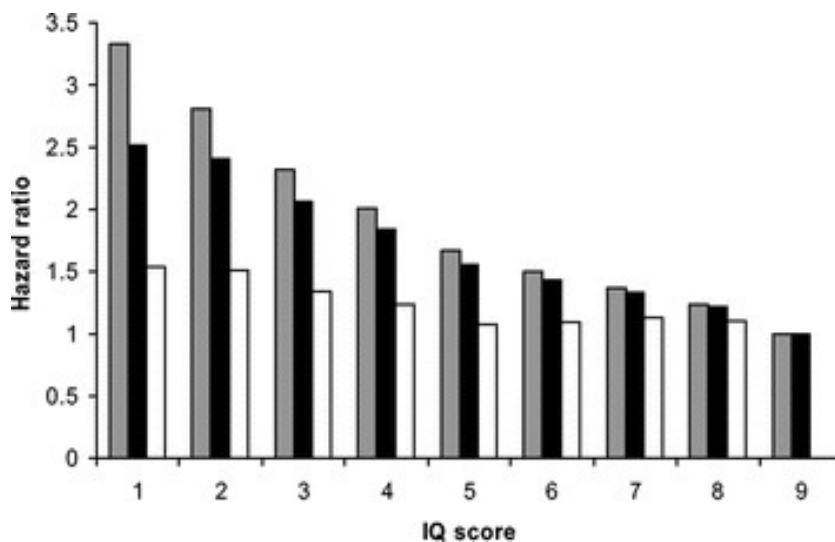


Figure 1-4. Hazard ratios for the relation of IQ score with total mortality (N = 994,262). Basic adjustment: age, year of birth, and conscription testing center (grey bars); full adjustment (age, year of birth, conscription testing center, parental social class, height, BMI, blood pressure, and illness) without education (black); full adjustments with education (white). The referent is the highest scoring IQ group (category 9). Reprinted with permission from Batty et al. (2009). Copyright 2009 by Wolters Kluwer Health.

Studies examining cause-specific mortality have found consistent results for the negative association between childhood cognitive ability and one of the world's major causes of death; coronary artery disease. For example, a study of 680,000 Swedish men who had their cognitive ability tested around age 18 found an inverse association between general cognitive ability and specific cognitive abilities, and death due to coronary artery disease (HR = 0.82, 95% CI = 0.79 – 0.85). This association was independent of childhood or adult socio-economic status (Silventoinen, Modig-Wennerstad, Tynelius, & Rasmussen, 2007). As shown in Figure 1-5, using the Danish Conscription Database, each SD decrease in cognitive ability was associated with an 36% higher risk of dying due to cardiovascular (HR = 1.36, 95% CI = 1.34 – 1.38) (G. T. Christensen et al., 2016). Results for one of the other major causes of death, cancer, have been inconsistent (Batty, Deary, & Gottfredson, 2007; Batty et al., 2009; G. T. Christensen et al., 2016; Wraw et al., 2015), and will not be discussed further in this thesis.

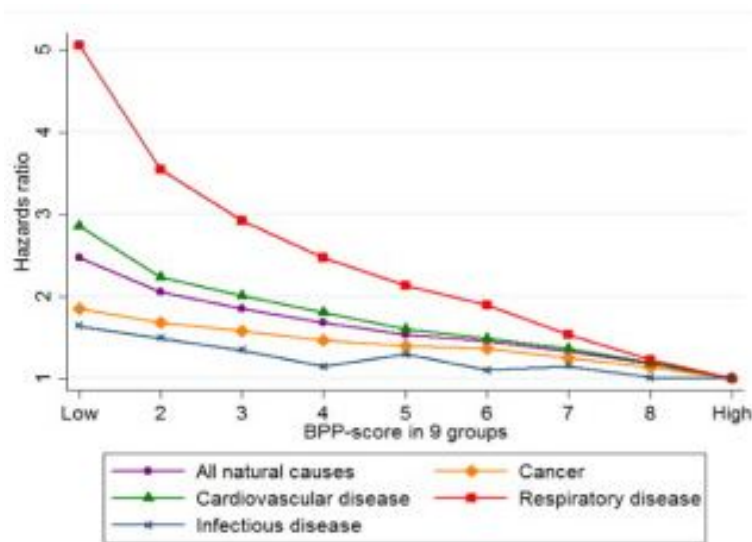


Figure 1-5. Age-adjusted hazard ratios for the associations between cognitive ability test score (Børge Prien Prøve (BPP)-score) in nine equal sized groups and cause-specific mortality in 662,185 men. Reprinted with permission from G. T. Christensen et al. (2016). Copyright by Elsevier.

1.2.2. Physical health

To better understand the underlying aetiology of the well-established link between cognitive ability and mortality, it is important to examine the association between cognitive ability and morbidity. This could strengthen the results of the mortality studies, due to the relatively uninformative nature of all-cause mortality studies with regards to the aetiology of the association, as well as the lack in power due to small numbers of deaths for cause-specific mortality. A study by Wraw et al. (2015), based on the National Longitudinal Study of Youth 1979 (NLSY-79), found that higher cognitive ability in youth is associated with better physical health at age 50 (OR = 1.70, 95% CI = 1.55 – 1.86). Most studies examining the association between cognitive ability and health outcomes focus on cardiovascular traits (Hart et al., 2004; Hemmingsson, Essen, Melin, Allebeck, & Lundberg, 2007) and mental health disorders (Dickson, Laurens, Cullen, & Hodgins, 2011; Zammit, Allebeck, David, & et al., 2004). The following Sections will, therefore, focus on cardiovascular disease and its risk factors, and mental health.

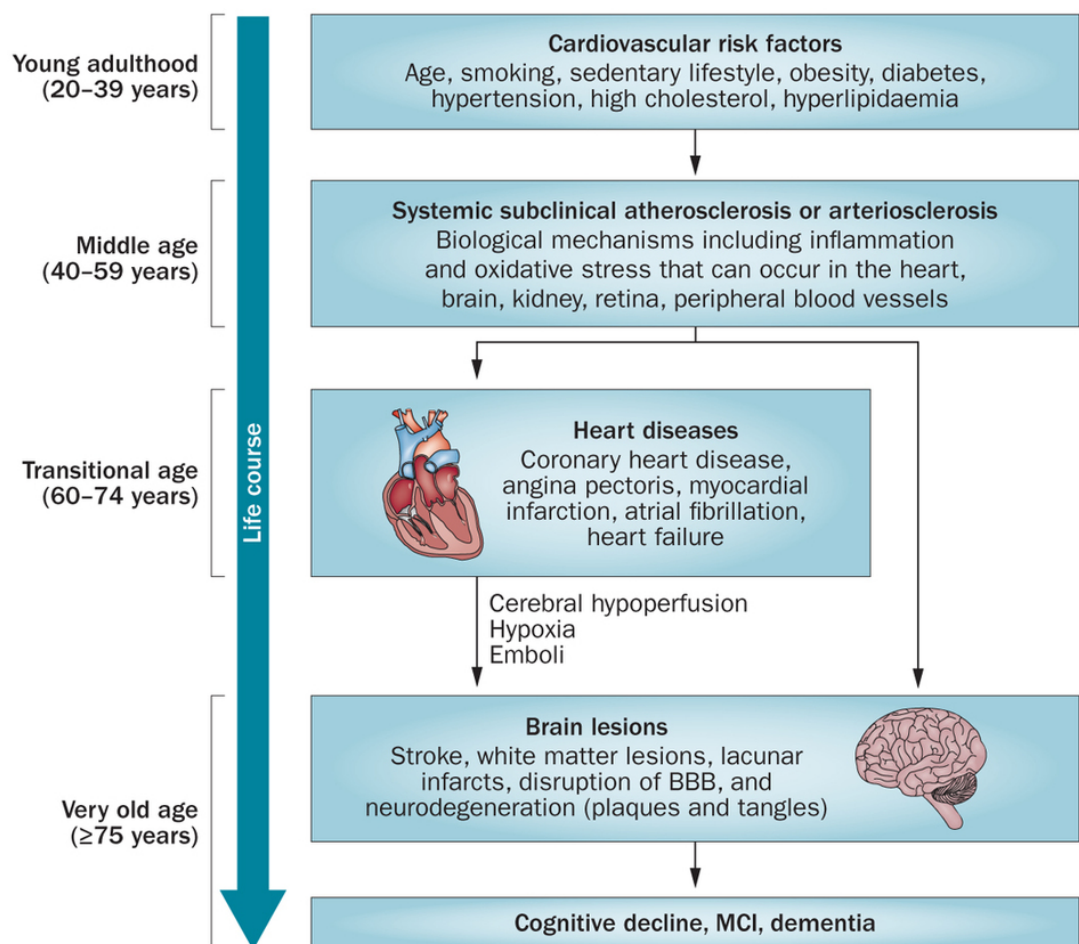
1.2.2.1. Cardiovascular disease

Higher cognitive ability has been linked to lower risk of cardiovascular disease and its risk factors. Batty, Mortensen, Nybo Andersen, and Osler (2005a) found a negative association between childhood cognitive ability and coronary artery disease (HR = 2.70, 95% CI = 1.60 – 4.57) in a sample of about 7000 Danish men. This association was not attenuated when controlling for childhood socioeconomic status. B. A. Roberts et al. (2013) examined the association between childhood cognitive ability and a subclinical precursor for coronary artery disease, i.e. intima-media thickness, in 1142 children from the Newcastle Thousand Families Study. Intima-media thickness is a measure for arterial wall thickness and when increased it is a form of atherosclerosis, and is associated with increased risk of coronary artery disease (Polak et al., 2011). The study by B. A. Roberts et al. (2013) found that higher general cognitive ability in childhood and better performance on specific tests for English and mathematics was associated with lower intima-media thickness (IMT) at age 50, a one SD increase in childhood cognitive ability was associated with a 0.039 mm lower IMT (95% CI - 0.080 to -0.002) in females and a 0.053 mm (95% CI -0.102 to -0.004) lower IMT in males. In a study of 5793 individuals based on the NLSY-79, higher childhood cognitive ability was associated with lower risk for cardiovascular disease (OR = 0.59, 95% CI = 0.48 – 0.73) (Wraw et al., 2015). The negative association between cognitive ability and cardiovascular disease supports the idea that vascular processes mediate the pathway between childhood cognitive ability and cognitive decline in late life.

Rostamian, Mahinrad, Stijnen, Sabayan, and de Craen (2014) examined the association between cognitive performance and risk of stroke in a meta-analysis of 12 studies including a total of 83,000 participants (3043 cases of stroke) and found an association between lower performance on tests of general cognitive ability, executive functioning, memory, and language, and higher risk of stroke. A smaller study by Batty et al. (2005a) in 7000 Danish

men (93 cases of stroke), did not find such association between childhood cognitive ability and risk of stroke, however this could be due to the lower number of stroke cases. Results from the NLSY-79 showed an inverse association between childhood cognitive ability and stroke (OR = 0.65, 95% CI = 0.52 – 0.81) (Wraw et al., 2015), supporting the findings by Rostamian et al. (2014).

The previous paragraph provided evidence for an association between lower childhood cognitive ability and higher risk for cardiovascular disease. However, it could also be possible that cardiovascular disease is a risk factor for cognitive decline in later life. Neuroimaging and autopsy studies have shown that vascular changes in the brain are associated with dementia (F. E. Matthews et al., 2009; Schneider, Arvanitakis, Leurgans, & Bennett, 2009). The Whitehall II study showed an association between prior coronary artery disease events and later cognitive ability, with lower scores on domains of reasoning, fluency and vocabulary that were independent of socio-economic status and medication (Singh-Manoux et al., 2008). A systematic review examining cognitive function in patients with coronary artery disease concluded that coronary artery disease is a risk factor for decline in general cognitive ability (Eggermont et al., 2012). These findings are supported by other epidemiological studies, as discussed by Qiu and Fratiglioni (2015), who suggested that cardiovascular disease and its risk factors potentially share pathological processes with cognitive ageing. Figure 1-6 shows the possible association between cardiovascular disease and cognitive decline. The association between childhood cognitive ability and later life cardiovascular disease has not been discussed in this paper, and it is possible that lifestyle cardiovascular risk factors in young adulthood are ‘caused’ by lower childhood cognitive ability.



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Figure 1-6. The heart–brain connection in ageing and cognitive decline. The schematic shows aetiological factors, pathophysiological mechanisms, and the sequence of events over the life-course of an individual. BBB, blood–brain barrier; MCI, mild cognitive impairment. Reprinted with permission from Qiu and Fratiglioni (2015). Copyright by Springer Nature 2015.

1.2.2.2. Cardiovascular risk factors

Two important risk factors for cardiovascular disease are type 2 diabetes (Shah et al., 2015) and high blood pressure (Kannel, 1996) and these are both also associated with cognitive ability. Cukierman, Gerstein, and Williamson (2005) examined the association between type 2 diabetes and cognitive ability in a systematic review including 25 longitudinal studies with a total of 8656 participants. They showed both a higher risk of cognitive decline as well as a greater rate of cognitive decline in type 2 diabetes patients. This supports the general consensus

that cognitive decline is a chronic complication of type 2 diabetes (Biessels, Deary, & Ryan, 2008; Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006). The association between cognitive ability and subsequent diabetes is less clear. A longitudinal study, using data from the Lothian Birth Cohort 1936, examined the association between childhood cognitive ability and subsequent type 2 diabetes (Möttus, Luciano, Starr, & Deary, 2013). The Lothian Birth Cohort 1936 (LBC1936) is a longitudinal study with the aim to identify determinants in normal cognitive ageing using data from the Scottish Mental Survey of 1947 (I. J. Deary et al., 2007). The Survey tested nearly all Scottish children (93.2%) born in 1936 using a validated test of general cognitive ability (Moray House Test, Number 12). Survivors of the study living in the Lothian area of Scotland were recruited for cognitive testing 60 years later at age 70 years, which provides the opportunity to assess change in cognitive ability over nearly a lifetime's duration. The study by Möttus et al. (2013) showed that participants with a diagnosis of type 2 diabetes, diagnosed using average plasma glucose levels measured by glycated haemoglobin (HbA1c), had lower performance on test of general cognitive ability in both childhood ($OR = 0.76$, 95% $CI = 0.64 - 0.92$) and older age ($OR = 0.78$, 95% $CI = 0.66 - 0.93$) (Möttus et al., 2013). Very similar results were found based a self-report measure of type 2 diabetes. This suggests that instead of cognitive decline being a chronic complication of type 2 diabetes, cognitive ability might contribute to the onset of type 2 diabetes, supporting the hypothesis of reverse causation. A large study of almost 6000 individuals supported this reverse causality hypothesis by showing that higher childhood cognitive ability (measured between age 14 and 21) was associated with lower risk of type 2 diabetes ($OR = 0.85$, 95% $CI = 0.77 - 0.93$), but this result became non-significant when adjusted for childhood and adult socio-economic status (Wraw et al., 2015). Twig et al. (2014) showed, in a sample of 35,500 young men from the Metabolic, Lifestyle and Nutrition Assessment in Young Adults (MELANY) cohort, that each point decrease on a 9-point cognitive ability scale was associated with a 10% increase in risk for diabetes ($HR = 1.10$, 95% $CI = 1.04 - 1.17$), after adjusting for age, BMI, fasting plasma glucose levels, white blood cell count, socio-economic status, and lifestyle risk factors.

Both high and low blood pressure have been associated with a decline in cognitive ability, especially in combination with other cardiovascular risk factors (Novak & Hajjar, 2010). Wolf et al. (2007) showed that lower cognitive performance on the domains of executive functioning and visual-motor skills in participants suffering from both hypertension and obesity. Similar results were found in the Atherosclerosis Risk in Communities (ARIC) study (Knopman, Mosley, Catellier, & Coker, 2009) and in the third National Health and Nutrition Examination Survey (NHANES III) study (Pavlik, Hyman, & Doody, 2005), showing lower cognitive ability in individuals with hypertension and other cardiovascular risk factors (such as diabetes and stroke). Wraw et al. (2015) found an association between lower levels of childhood cognitive ability and hypertension (OR = 0.80, 95% CI = 0.75 – 0.86), independent of both childhood and adult socio-economic status. The findings for hypotension are inconsistent, with some studies finding lower cognitive ability in participants with hypotension, while others find no effect (Novak & Hajjar, 2010).

To summarize, studies have indicated a relationship between cardiovascular disease, including cardiovascular risk factors, and cognitive ability, with both lower cognitive ability being associated with higher risk for cardiovascular diseases, as well as cardiovascular diseases as a risk factor for later life cognitive decline. No consistent evidence has been found so far to indicate a direction of effect for this association, it is therefore important that studies examine the potential direction of effect between cognitive ability and cardiovascular disease.

1.2.2.3. Dementia

A decline in cognitive ability is part of non-pathological cognitive ageing, but it can also be a symptom of pathological cognitive decline. Whalley et al. (2000) examined the association between childhood cognitive ability and dementia using data from the Scottish Mental Survey

1932, and found that participants with late-onset dementia had lower childhood cognitive ability ($p < 0.03$). A large follow-up, using the same sample, reported that lower childhood cognitive ability was a risk factor for late-onset vascular dementia (OR = 0.62, 95% CI = 0.41 – 0.94), but not for Alzheimer's type dementia (OR = 0.97, 95% CI = 0.79 – 1.19) (McGurn, Deary, & Starr, 2008). These findings indicate vascular processes potentially mediate the association between childhood cognitive ability and cognitive decline in later life. The findings also provide support for the idea of reverse causation, which suggests that pathological disease leads to cognitive decline.

1.2.3. Mental health

The other highly relevant link between cognitive ability and health is the one with mental health. Mental health problems are an important cause of disability in the world, with one in six English adults suffering from a common mental disorder, which are more common in females (one in five) than in males (one in eight) (McManus, Bebbington, Jenkins, & Brugha, 2016).

Mood disorders, such as major depressive disorder and bipolar disorder, are commonly associated with cognitive impairment on the domains of memory, executive functioning and processing speed, however the direction of the association is not clear. A large cohort study of around 50,000 Swedish men showed that lower performance on tests of premorbid general intelligence was associated with higher risk of developing schizophrenia and depression, but not bipolar disorder (Zammit et al., 2004). Wraw et al. (2016) showed a potential protective effect of intelligence on mental health in middle age. They found that higher childhood intelligence was associated with fewer depressive symptoms [$\beta = -0.16$, 95% CI = -0.19 – (-0.12)] measured by the 7-item Center for Epidemiological Studies Depression Scale, and better overall mental health state at age 50 (OR = 0.78, 95% CI = 0.72 – 0.85), but also with a higher

lifetime self-reported diagnosis of depression (OR = 1.11, 95% CI = 1.01 – 1.22). Various longitudinal studies have found an association between lower childhood cognitive ability and increased risk of mental health disorders (Batty, Mortensen, & Osler, 2005b; Gale, Batty, Tynelius, Deary, & Rasmussen, 2010; Gale et al., 2008; Gale, Hatch, Batty, & Deary, 2009; Koenen et al., 2009; Walker, McConville, Hunter, Deary, & Whalley, 2002). The largest study, including over 1 million men from the Swedish Conscript Study, showed an association between lower childhood cognitive ability and greater hospitalization risk for eight different mental health disorders (Gale et al., 2010). Each SD decrease in cognitive ability was associated with a 60 % (HR = 1.60, 95% CI = 1.55 – 1.65) increased risk of being admitted for schizophrenia, as well as a 50 % (HR = 1.50, 95% CI = 1.47 – 1.51) increased risk for mood disorders. Figure 1-7 shows the hazard ratios for hospital admission for both schizophrenia and mood disorders, as well as other mental health disorders, according to a nine-point scale for cognitive ability.

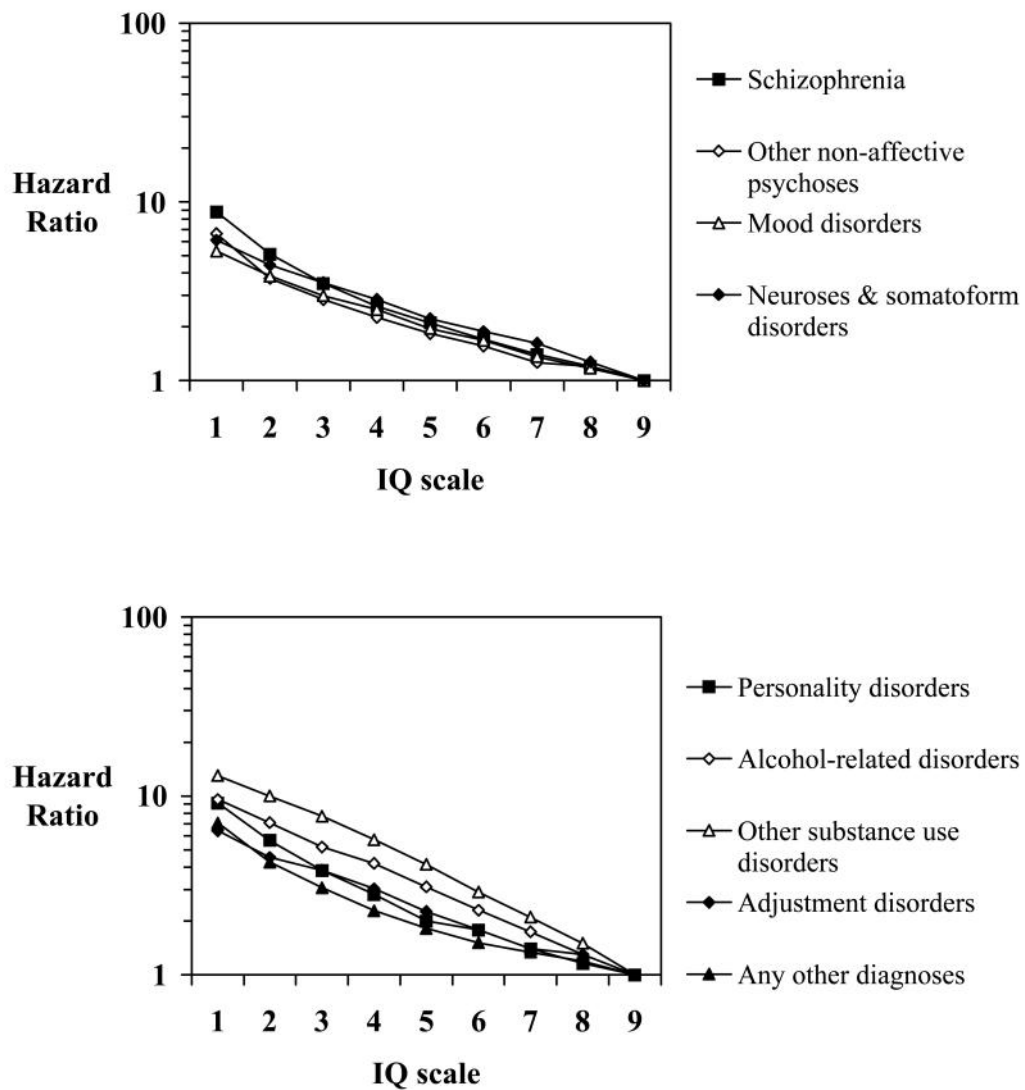


Figure 1-7. Hazard ratios for admission for different categories of mental health disorders, according to nine-point scale of cognitive ability (IQ scale). Reprinted with permission from Gale et al. (2010). Copyright by Lippincott, Williams and Wilkins.

Lower cognitive ability was also associated with increased risk of multiple diagnoses, for a 1 SD decrease in cognitive ability, the OR for receiving multiple diagnoses ranged from 1.71 (95% CI = 1.68 – 1.73) for two or more diagnoses, to 2.06 (95% CI = 1.91 – 2.22) for six or more diagnoses (Gale et al., 2010).

A meta-analysis of 29 longitudinal studies, including 121,749 individuals, showed that the correlation between higher cognitive ability and lower risk of subsequent major depressive disorder was attenuated from -0.09 [95% CI = -0.13 – (-0.05)] to -0.03 (95% CI = -0.08 – 0.01)

after adjusting for baseline depression symptoms (Sculpt et al., 2017), which indicates that symptoms of major depressive disorder have an effect on cognitive performance at the time of measurement, rather than cognitive ability being a risk factor for subsequent major depressive disorder.

Multiple studies have shown the impact of schizophrenia on cognitive performance, as well as an association between lower childhood cognitive abilities and increased risk of schizophrenia (Dickson et al., 2011; McIntosh, Harrison, Forrester, Lawrie, & Johnstone, 2005; Osler, Lawlor, & Nordentoft, 2007). The neurodevelopmental theory of schizophrenia hypothesizes that cognitive deficits in schizophrenia arise prior to the onset of the disease. McIntosh et al. (2005) showed an impairment in both general, verbal and premorbid intelligence in 74 schizophrenia patients and their unaffected relatives. A meta-analysis of 23 studies including youths under 16 years old, who later developed schizophrenia, examined the association between different cognitive abilities and later schizophrenia diagnosis (Dickson et al., 2011). This study showed lower cognitive ability scores and impaired motor skills in youths who later developed schizophrenia, compared to healthy controls. No difference was found between schizophrenia patients and healthy controls in general academic achievement and mathematical achievement. A study by Kendler, Ohlsson, Mezuk, Sundquist, and Sundquist (2016) found that lower cognitive performance is not a strong risk factor for schizophrenia, but that the deviation in cognitive performance from family cognitive performance, measured by both general intelligence and academic achievement, is a stronger risk factor for schizophrenia.

Bipolar disorder has been linked to cognitive decline, but findings on this association have been non-specific, with great heterogeneity in effect sizes (Bourne et al., 2013).

Similar to the association between physical health and cognitive ability, mental health has been linked to cognitive ability. Several studies have shown mental health disorders to be a risk factor for cognitive decline, as well as lower childhood cognitive ability as a risk factor for mental health disorders in later life. In order to better understand pathways between mental health and cognitive disorders, it is important to examine the direction of effect for this association.

1.2.4. Cognitive ability and health mechanisms

All cognitive epidemiology studies to date have contributed to the progress in understanding the aetiology between cognitive ability and health. The exact mechanisms, however, remain unclear. There are multiple mechanisms that could underlie this association, for example the theory of system integrity (I. J. Deary, 2012), the disease management hypothesis, and the disease prevention hypothesis (Whalley & Deary, 2001). These and other potential pathways between premorbid cognitive ability and mortality are displayed in Figure 1-8 (Batty et al., 2007). Batty et al. (2007) suggest that genetic analyses will provide further insight in to the pathways between premorbid cognitive ability and mortality. Findings from genetic analysis between cognitive ability and health will be discussed in Section 1.3 of this Chapter.

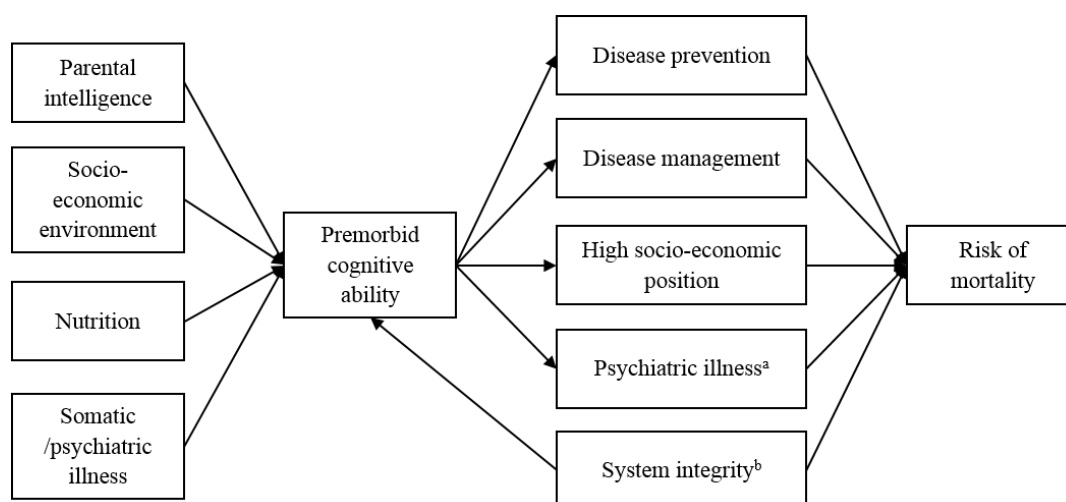


Figure 1-8. Simplified model of influences on pre-morbid IQ and potential pathways linking pre-morbid IQ with later mortality. ^a Although psychiatric disease is shown as a mediating variable between IQ and mortality, it might also be an antecedent variable if, for example, suboptimal neurodevelopment were the prior cause of both psychiatric disease and early mortality. Both of these possibilities are captured in the text. ^b Note that system integrity is shown as antecedent to both IQ and mortality. In this pathway, lower IQ is not a cause of mortality, but both IQ and mortality are influenced by this more fundamental physiological integrity. Adapted with permission from Batty et al. (2007). Copyright by Elsevier 2007.

The theory of bodily system integrity suggests that the negative association between cognitive ability and health may be explained by an individual's physiological make-up (I. J. Deary, 2012). Higher childhood cognitive ability might be a characteristic of a 'well-wired' body that is better at handling environmental challenges, and might therefore covary with disease risk instead of being a causal risk factor for disease. This association also works the other way around; lower childhood cognitive ability could reflect a body that is less adapted to handle environmental challenges.

The disease management hypothesis provides an explanation for the lower disease rates in individuals with better cognitive abilities, suggesting that these individuals are better at managing their existent diseases. As written by Gottfredson (2004), health self-care is a cognitive competence. Individuals with better cognitive ability are likely to better understand and remember medical advice, as well as recognizing symptoms that require further medical

attention. This hypothesis has been supported by multiple studies finding an association between better cognitive ability and treatment adherence (I. J. Deary et al., 2009; Stilley, Bender, Dunbar-Jacob, Sereika, & Ryan, 2010). Using data from the Aspirin for Asymptomatic Atherosclerosis (AAA) study, a randomized controlled trial including 1993 individuals, I. J. Deary et al. (2009) examined the association between cognitive ability and treatment adherence. The study showed that individuals with higher cognitive ability were more likely to continue treatment during a two-year observational period, one SD advantage in cognitive ability was associated with a 25% lower risk of stopping medication ($HR = 0.75$, $95\% CI = 0.64 - 0.75$). Similar results have been found in a study showing that better cognitive performance on tests of memory, attention and executive function was associated with better medication adherence (Stilley et al., 2010).

The disease prevention hypothesis suggests an association between higher cognitive ability and better health outcomes due to the association with better social status and healthier lifestyle choices. For example, studies have shown that children with better cognitive ability were less likely to start smoking (Martin, Fitzmaurice, Kindlon, & Buka, 2004) and more likely to stop smoking in adulthood (Taylor et al., 2003). This is relevant in the association between cognitive ability and physical health, as smoking is a risk factor for cardiovascular diseases (US Department of Health and Human Services, 2014).

Childhood socioeconomic status can be seen as a possible confounder of the association between cognitive ability and health. However, most studies discussed in the previous Section show little or no attenuation when adjusting for childhood socioeconomic status, measures by parental income or social class (Calvin et al., 2011; Wraw et al., 2015). This suggests that the individual differences in childhood cognitive ability act independently from the individual differences in childhood social class to predict health outcomes.

Individual differences in adult socioeconomic status may explain more of the association between childhood cognitive ability and health than childhood socioeconomic status. It is hypothesized that cognitive ability has an effect on adult socioeconomic status, measured by education, income and adult social class, with adult socioeconomic status being a mediator of the cognitive ability and health association (Batty et al., 2007). Previously discussed studies have shown an attenuation of the cognitive ability and health association when adjusting for adult socioeconomic status (Calvin et al., 2011; Wraw et al., 2015), supporting the hypothesis that adult socioeconomic status is a mediator of the association between cognitive ability and health. One explanation for this is that the protective effects of higher childhood cognitive ability build up during the lifetime. Higher childhood cognitive ability potentially leads to more educational success, better social status and thus better access to healthcare, which in turn leads to better health (I. J. Deary, 2010).

1.3. Cognitive ability and health: genetics

Section 1.2.4 of this Chapter described different mechanisms potentially underlying the association between cognitive ability and health. Many studies have shown a familial aspect indicating that genetics could also play an important role in the aetiology of cognitive ability and its associations with health outcomes (Plomin, DeFries, Knopik, & Neiderhiser, 2016). In order to better understand the associations between cognitive ability and health, it is central to first understand the genetic aetiology of cognitive ability. This Section of Chapter 1 will therefore start by describing common techniques to test for a shared genetic aetiology, followed by empirical work examining the genetic aetiology of cognitive ability using both behavioural genetic as well as molecular genetic studies. This Chapter will finish with the shared genetic aetiology between cognitive ability and health outcomes.

1.3.1. Genetic methodologies

1.3.1.1. Behavioural genetics

The study of the biological basis of individual differences is known as behavioural genetics. This area assesses the effect of genetic and environmental factors on different traits, such as cognitive ability, using for example family, adoption, and twin studies. Family studies are generally unable to distinguish genetic effects from shared environmental effects, unless the study consists of large families with different degrees of relatedness (Falconer & Mackay, 1996). Adoption and twin studies can be used to disentangle the genetic aetiology of traits, by identifying and separating genetic and shared and non-shared environmental effects (Falconer & Mackay, 1996). Francis Galton was a pioneer in the field of behavioural genetics; he conducted one of the first studies showing a familial resemblance in cognitive ability (Galton, 1869). The field of behaviour genetics, specifically Eric Turkheimer, has come up with three ‘laws’ of behaviour genetics (Turkheimer, 2000), which are:

1. All human behavioural traits are heritable.

2. The effect of being raised in the same family is smaller than the effect of genes.
3. A substantial portion of the variation in complex human behavioural traits is not accounted for by the effects of genes or families.

The first and third 'law' have been shown to be accurate, in particular by a large meta-analysis of all human twin studies over the past fifty years (Polderman et al., 2015). The second 'law' might not be accurate in traits with low heritability estimates, in which case the effect of being raised in the same family could be higher than effect of genes. (Polderman et al., 2015)

The familial aspect of traits such as cognitive ability can be studied using the adoption design. Non-adoptive families consist of individuals who are genetically related and have a shared environment, while adoptive families also have a shared environment, but are not genetically related. This creates the opportunity to study the genetic and environmental sources of a trait. Similarities between the adopted child and its biological parents are due to genetic reasons only, whereas the similarities between the adopted child and its adopting parents are due to shared environment only (Plomin & Daniels, 2011). Early adoption studies showed that the correlations for cognitive ability were stronger in non-adoptive families than in adoptive families, which indicates a genetic effect (Burks, 1928; Leahy, 1935).

As mentioned at the beginning of this Section, another behavioural genetics design to disentangle the genetic aetiology of a trait is a twin study. Twin studies examine the resemblance of monozygotic (MZ) twins, who are genetically identical, with same-sex dizygotic (DZ) twins, who share, on average, 50 % of their genetic information. A classic twin study splits the phenotypic variance in three components; the additive genetic (A) component, the common or shared environmental component (C), and the unique or non-shared environmental (E) component. As MZ twins are genetically identical, both A and C are assumed to have a correlation of 1, whereas DZ twins only shared around 50% of their genes, which means that C is assumed to correlate at one, and A only at 0.5. E is assumed to be

uncorrelated between twins and contributes to the differences within pairs. If a trait is influenced by genetic factors, it is expected that the correlation between MZ twins is stronger than the correlations between DZ twins. An important part of twin studies is the ‘equal environments assumption’, which assumes that twins raised in the same family share the same environment (Plomin & Daniels, 2011). A violation of this assumption would inflate the genetic influence estimates, but it has been shown that this assumption is valid for most traits (Derks, Dolan, & Boomsma, 2006).

1.3.1.2. Heritability

Twin and adoption studies use familial resemblance to estimate the genetic influence on traits, but molecular genetic methods enable scientists to estimate identify specific genes affecting a trait by using DNA instead of familial resemblance. Molecular genetic methods can also be used to estimate the heritability across many genetic variants, using DNA in unrelated individuals; this method is referred to as Genome-wide Complex Trait Analysis (GCTA-GREML) (Yang, Lee, Goddard, & Visscher, 2011). GCTA-GREML uses the genetic similarity between each pair of, say, thousands of unrelated individuals to predict phenotypic similarity (Jian Yang et al., 2010; Yang et al., 2011). The genetic similarity between pairs is based on the similarity across hundreds of thousands of single nucleotide polymorphisms (SNPs) across the genome, leading to millions of pair comparisons. These polymorphisms are single base pair substitutions and are the most common form of genetic variation in individuals (The 1000 Genomes Project Consortium, 2010). Pairs of individuals with a genetic similarity greater than the level of fifth degree relatives are removed from the analysis to ensure that all pairs are effectively unrelated. Heritability estimates derived using GCTA-GREML to date are limited by the fact that they have used only common SNPs, with allele frequencies above 1%, instead of all genetic variants such as in twin studies, and as such they provide the lower bound heritability estimate.

1.3.1.3. Linkage analysis and candidate gene studies

Linkage analysis can be used to identify regions of a chromosome that are associated with a disorder or trait, by analysing how genetic markers segregate with a trait in a family. This approach has been successful in identifying genetic variants involved in rare disorders such as cystic fibrosis (Kerem et al., 1989) or Huntington disease (MacDonald et al., 1992). When applying this method to complex traits such as cognitive ability, linkage analysis has been less successful due to the number of genetic variants each with small effects involved.

While linkage analysis is unable to detect linkage for genes of small effect, candidate gene studies are able to detect these small effects. Candidate gene studies focus on associations between genetic variation within pre-specified genes. These genes are selected based on a prior hypothesis, for example in the case of cognitive ability, candidate genes were selected based on neurotransmitter genes involved in disease, or based on developmental and metabolic processes.

1.3.1.4. Genome-wide association studies

Genome-wide association studies (GWAS) test for an association between single SNPs and traits by evaluating the correlation between a trait and the allele frequency of a SNP (Bush & Moore, 2012). GWAS are based on the principle of linkage disequilibrium (LD) in the population. LD measures the non-random assortment of alleles at two loci. If allele A at locus 1 and allele B at locus 2, with a population frequency of p_A and p_B respectively, are independent of each other, the allele frequency for the haplotype AB would be $p_A p_B$ (Pritchard & Przeworski, 2001). These two alleles would be in LD when the population frequency is higher or lower than the expected population frequency. Ancestrally older populations (such as the African population) have smaller regions of LD, due to the accumulation of more

recombination events, than ‘younger’ populations such as European or Asian populations (Bush & Moore, 2012).

GWAS have been very successful in identifying associations between traits and genetic variants, such as height (Wood et al., 2014), BMI (Locke et al., 2015), schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), and educational attainment (Okbay et al., 2016b). The effect size of the association between a particular SNP and the trait is generally very small, both in terms of the amount of variance explained and the beta effect. As shown in Figure 1-9, in a GWAS of educational attainment (as measured by years of education), the amount of variance explained by the 74 genome-wide significant SNPs ($p < 5 \times 10^{-8}$) ranged between 0.01 % and 0.04 % with effect sizes ranging from 0.01 to 0.05 SD per allele (Okbay et al., 2016b). At the other end of the spectrum, the top (highest significance) SNPs for height and BMI explain ~0.28 % and 0.33% of the variance, respectively.

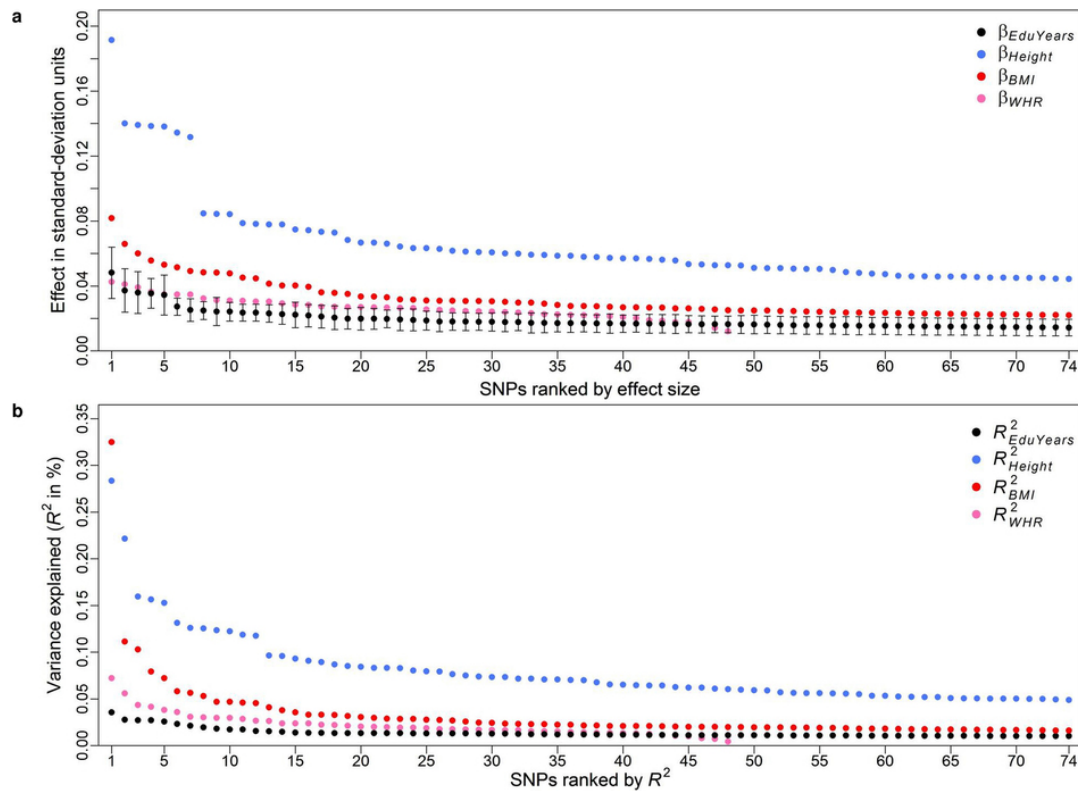


Figure 1-9 . a, SNPs ordered by absolute value of the standardized effect of one more copy of the education-increasing allele, with 95% confidence intervals. b, SNPs ordered by R^2 . Effects on EduYears are benchmarked against the top 74 genome-wide significant hits identified in the largest GWAS conducted to date of height and body mass index (BMI), and the 48 associations reported for waist-to-hip ratio adjusted for BMI (WHR). These results are based on the GIANT consortium's publicly available results for pooled analyses restricted to European-ancestry individuals: https://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium. Reprinted with permission from Okbay et al. (2016b). Copyright 2016 by Springer Nature.

The possible shared genetic aetiology between cognitive ability and health can be assessed using both behavioural genetic and molecular genetic techniques, the main molecular genetic techniques that will be discussed in the next Sections are linkage disequilibrium score regression (LDSR), polygenic risk score analysis (PRS), and Mendelian randomization analysis (MR).

1.3.1.5. Pleiotropy

The previous Section described different techniques to examine the genetic aetiology of traits. The main focus on this thesis is, however, the shared genetic aetiology between cognitive ability and health, and between negative emotions and health. The phenotypic link between these traits is possibly caused by pleiotropic genetic variants. Pleiotropy describes the phenomenon that one gene contributes to multiple phenotypic traits, and it consists of different subtypes, as shown in Figure 1-10. The work in this Thesis will mainly focus on biological and mediated pleiotropy. Biological pleiotropy is the result of the same genetic variants being involved in two traits, while mediated pleiotropy describes the situation of two traits causally associated with each other where a genetic variant affects the first trait, which then causally affects the second trait.

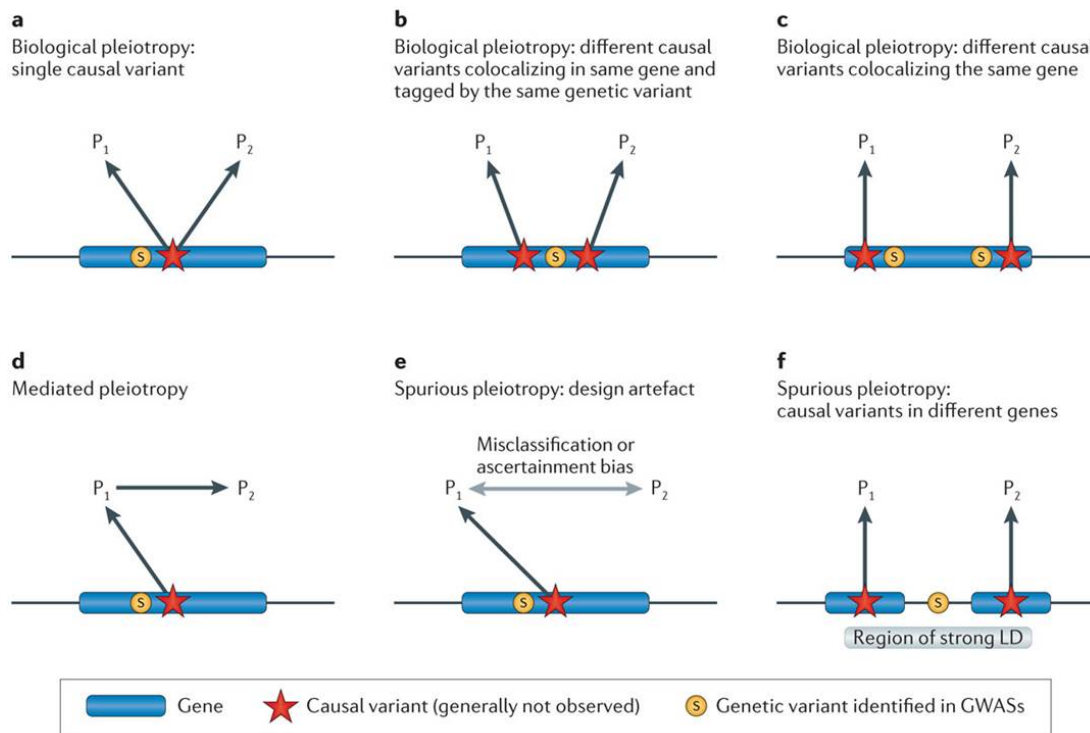


Figure 1-10. In each scenario, the observed genetic variant (S) is associated with phenotypes 1 and 2 (P_1 and P_2). We assume that the observed genetic variant is in linkage disequilibrium (LD) with a causal variant (red star) that affects one or more phenotypes. In some cases, the causal variant may be identified directly and the figures can be simplified accordingly. The various figures correspond to the unobserved underlying pleiotropic structure. **a** | Biological pleiotropy at the allelic level: the causal variant affects both phenotypes. **b** | Colocalizing association (biological pleiotropy): the observed genetic variant is in strong LD with two causal variants in the same gene that affect different phenotypes. **c** | Biological pleiotropy at the genic level: two independent causal variants in the same gene affect different phenotypes. **d** | Mediated pleiotropy: the causal variant affects P_1 , which lies on the causal path to P_2 , and thus an association occurs between the observed variant and both phenotypes. **e** | Spurious pleiotropy: the causal variant affects only P_1 , but P_2 is enriched for P_1 owing to misclassification or ascertainment bias, and a spurious association occurs between the observed variant and the phenotype 2. **f** | Spurious pleiotropy: the observed variant is in LD with two causal variants in different genes that affect different phenotypes. GWAS, genome-wide association study. Reprinted with permission from Solovieff, Cotsapas, Lee, Purcell, and Smoller (2013). Copyright by 2013 by Springer Nature.

1.3.1.6. Linkage disequilibrium score regression

LDSR is used to test for genetic overlap between traits, by using information from GWAS summary statistics (Brendan K. Bulik-Sullivan et al., 2015b). It relies on the fact that the effect-size estimate from the GWAS for a certain SNP incorporates the effects of all SNPs that are in LD with that SNP, and uses this to compute a genetic correlation between two traits of interest. For polygenic traits, SNPs in regions of high LD will be able to measure a greater proportion of the genome than SNPs in low LD regions, and will therefore have a higher χ^2 statistics than the SNPs in low LD regions. SNPs in higher LD with causal variants will also have a higher probability to tag the causal variant. LDSR uses the LD pattern in known populations to compute the genetic correlations from separate GWAS of different traits by using the standardized effect size (z-score) of the association between each SNP and a trait. By regressing the product of z-scores onto the LD score, the genetic covariance can be estimated (Brendan K. Bulik-Sullivan et al., 2015b). Genetic correlations reflect the correlation in additive genetic components. Using these correlations, one can calculate the co-heritability of two traits, i.e. the covariance between two traits on the same scale as the heritability, using the following formula: $r_g * \sqrt{(h_x^2 * h_y^2)}$, where r_g is the genetic correlation, and $h_{x/y}^2$ represents the heritability estimate of the two traits the genetic correlation is based on (Falconer & Mackay, 1996). Genetic correlations, as with any correlations, can be explained in multiple (and not mutually exclusive) ways: it might be that the genes cause both traits, biological pleiotropy, or it might be that there is mediated pleiotropy, where the gene affects one trait which then affects others. Some traits are more likely to be mediated pleiotropy (such as education, which is not measured biologically), whereas some are more likely—though, not certain—to be biological pleiotropy. While pleiotropy is one of the explanations for the existence of genetic correlations; genetic correlations are also possible in the absence of pleiotropy due to LD between variants found within the same gene boundaries (i.e. spurious pleiotropy).

1.3.1.7. Polygenic risk score analysis

The theory of polygenic inheritance states that most complex traits are affected by multiple loci, all of which contribute a small amount to the variation in the trait, previously described by Chabris, Lee, Cesarini, Benjamin, and Laibson (2015) as the fourth law of behavioural genetics. When performing a traditional GWAS the many loci with small effects will be indistinguishable from noise, but together these loci can account for a substantial proportion of the variation in the risk for a disease. This can be identified by PRS, by summarizing the variation across all loci into polygenic risk scores and examining the association between the polygenic risk score and the outcome variable in an independent sample (Purcell et al., 2009). In order to create PRS, several steps have to be performed. First, independent SNPs, based on the summary results from an independent GWAS, are identified by performing linkage disequilibrium clumping. This process forms ‘clumps’ of SNPs that are in LD with an ‘index’ SNP. The index SNP is the SNP with the lowest p-value in a predefined region (for example 250kb). All SNPs in LD with the index SNP, e.g. SNPs with an r^2 above a certain value, are then assigned to the clump. The next index SNP will be the following SNP with the lowest p-value that is not in LD with the previous index SNP. Secondly, all independent SNPs below different thresholds of p-values (e.g. 0.01, 0.05, 0.1, 0.5 and all SNPs) are identified. PRS are then created for each individual representing the net predictive effect of all reference alleles at each different threshold that an individual possesses from the discovery results. PRS are based on common SNPs that have been genotyped and therefore do not necessarily accurately tag causal variants. The associations between the SNPs and the outcome measure will be estimated with sampling error as the association is based on a finite sample. Due to this the amount of variance explained by PRS is usually relatively small and will never correspond to the heritability estimate for a trait, but it should be considered the minimum amount of variance explained. It is important to note that independence of the two samples (GWAS and prediction)

is crucial, as PRS are created based on SNPs in approximate linkage equilibrium based on arbitrary thresholds, which can also bias the amount of variance explained (Wray et al., 2013). In this Thesis, the term polygenic risk scores will be used for disorders, while polygenic profile score will be used for non-disorder-based traits (such as cognitive ability or negative emotions).

1.3.1.8. Mendelian randomisation

LDSR and PRS identify possible shared genetic aetiology between traits, however these techniques do not inform on possible causality between traits. Identifying the underlying causes of the associations between cognitive ability and health is one of the fundamental aims of the field of cognitive epidemiology. Mendelian randomization (MR) is a technique that can be used to identify causal associations. MR utilizes genetic variants as instrumental variables for a modifiable exposure (e.g. BMI) in order to estimate the causal effect of that exposure on an outcome (e.g. cognitive ability). The instrumental variables should predict the exposure and the outcome only through the exposure. Biological pleiotropy (as described in Section 1.3.1.5) violates these assumptions, while mediated pleiotropy does not violate these assumptions due to the idea that the genetic variant is associated with a trait, which is then associated with a second trait. GWAS summary statistics can be used to perform MR analysis, for example by using inverse variance weighted regression (IVW). IVW estimates the causal effect of the exposure on the outcome using the ratio of two “vectors”. These so-called vectors are based on the GWAS summary statistics of the gene variant – outcome association estimate (β) and the gene variant – exposure association estimate (β). The study in the current Thesis (Section 4.3) will use multiple SNPs for each instrumental variable, which means that the two vectors consists of a “list” of SNPs for the exposure with their respective effect estimates for the association and a list of those same SNPs with the effect estimate based on the association with the outcome. These two vectors are then regressed on each other, corrected for minor

allele frequency, by weighing the association by the standard error of the genetic variant – outcome association.

1.3.2. Genetic aetiology of cognitive ability

1.3.2.1. Adoption and twin studies

Adoption, twin, and family studies have estimated the heritability of cognitive ability, the amount of variance accounted for by genetic factors, to be between 40-80% with most evidence based on twin studies (Davis, Haworth, & Plomin, 2009; Haworth et al., 2010; Plomin et al., 2016; Plomin, Fulker, Corley, & DeFries, 1997; Polderman et al., 2015). A meta-analysis of all published twin studies in the past 50 years, which included almost 450,000 twin pairs for general cognitive ability, showed a heritability estimate of 47% for cognitive ability (Polderman et al., 2015). Haworth et al. (2010) showed, in a cross-sectional study of 11,000 twins, that the heritability of general cognitive ability increases significantly from 41% in childhood, to 55% in adolescence to 66% in young adulthood. Lyons et al. (2009) examined the heritability of cognitive ability in a longitudinal twin study of adult men and showed that the heritability increased from 49% at age 20 to 57% at age 55. The phenotypic correlation between cognitive ability at age 20 and at age 55 was 0.74, and 71% of this phenotypic correlation was due to additive genetic effects, 22% was due to shared environmental influences, and 6% was due to non-shared environmental influences. The study also reported a genetic correlation of 1 between the two measures of cognitive ability, which suggests that the same genetic variants influence cognitive ability both at age 20 and at age 55. A small twin study of 110 MZ twins and 130 DZ twins aged 80 years or older estimated the heritability of cognitive ability to be 62% while shared and non-shared environment account for 15% and 22% of the variance respectively (McClearn et al., 1997). A large meta-analysis, including 15 samples of longitudinal twin and adoption studies, replicated these findings by showing a low genetic stability in very early life, with strong increases over childhood, stabilizing in

adulthood (Tucker-Drob & Briley, 2014). In very early childhood, the greatest proportion to the phenotypic stability of cognitive ability is the shared environment (C), but with age, this contribution becomes smaller, while contribution by genes (A) increases greatly with age (Figure 1-11).

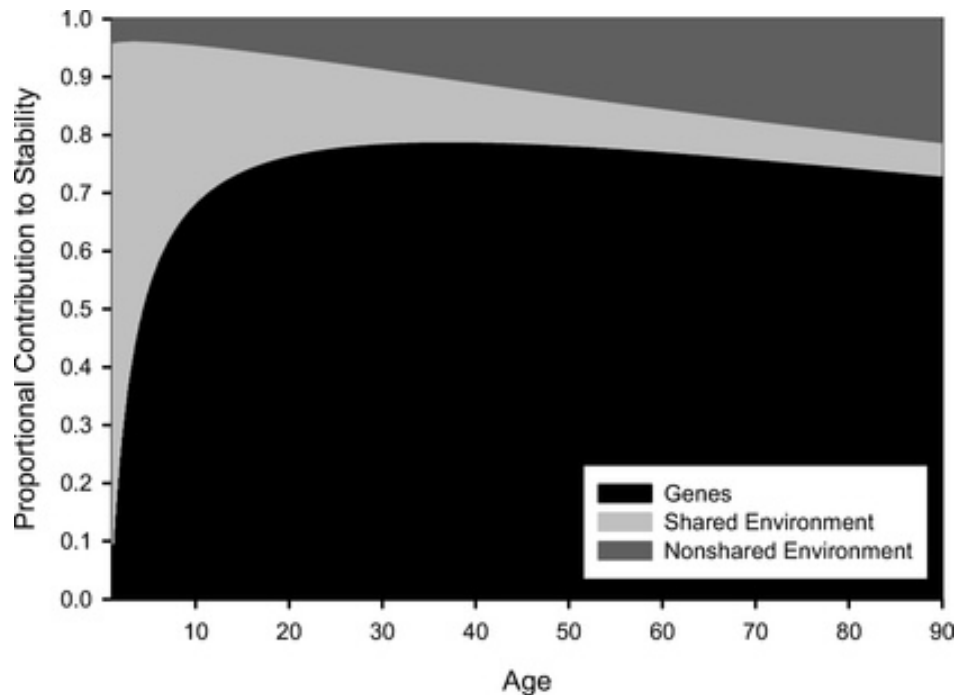


Figure 1-11. Proportional genetic, shared environmental, and nonshared environmental contributions to stability across the life span. Estimates are based on expectations from the best fitting continuous models. Reprinted with permission from Tucker-Drob and Briley (2014). Copyright by American Psychological Association 2014.

1.3.2.2. Molecular genetics

Multiple studies have estimated the SNP-based heritability (h^2_{SNP}) of cognitive ability in both childhood and adulthood (Benyamin et al., 2014; G. Davies et al., 2015a; G. Davies et al., 2016b). Benyamin et al. (2014) reported the h^2_{SNP} for childhood cognitive ability in three different cohorts, the Avon Longitudinal Study of Parents and Children (ALSPAC, $N = 5517$), the Twins Early Development Study (TEDS, $N = 2794$), and the University of Minnesota study (UMN, $N = 1736$). Common SNPs accounted for 46% (SE 6%), 22% (SE 10%), and 40% (SE

21%) of the variance in childhood cognitive ability in the ALSPAC, TEDS, and UMN cohorts respectively. Both TEDS and UMN are likely to be underpowered to provide a valid h^2_{SNP} estimate due to the smaller sample sizes compared to ALSPAC, as indicated by the size of the SEs. GCTA requires very large sample sizes (at least several thousand individuals) to be able to extract a small signal of genetic similarity from the noise of hundreds of thousands of SNPs (Visscher et al., 2014). G. Davies et al. (2015a) reported the h^2_{SNP} of general cognitive ability in later life to be 29% (SE 5%) and 28% (SE 7%) in the Atherosclerosis Risk in Communities Study (ARIC, N = 6617) and Health and Retirement Study (HRS, N = 5976) cohorts. These estimates have been replicated in the UK Biobank, showing a h^2_{SNP} of 31% (SE 2%) for a measure of general cognitive ability in a sample of 36,035 individuals (G. Davies et al., 2016b).

1.3.2.3. Linkage analysis and candidate gene studies

Linkage analysis of cognitive ability identified linkage with regions implicated in reading disability and autism (Dick et al., 2006; Doyle et al., 2008; Luciano et al., 2006; Posthuma et al., 2005), however these results have not been replicated. Many candidate genes have been identified for cognitive ability, as discussed in detail by Payton (2009), but most have not been replicated (Chabris et al., 2012; Houlihan et al., 2009; Mandelman & Grigorenko, 2012). *APOE* is the only candidate gene that has been replicated in a meta-analysis of 77 studies including 40,942 individuals (Wisdom, Callahan, & Hawkins, 2011). This meta-analysis showed that carriers of *APOE* $\epsilon 4$ performed significantly poorer on measures of general cognitive ability, memory, processing speed, and executive function, compared to *APOE* $\epsilon 4$ non-carriers. The results also indicated that the difference between $\epsilon 4$ carriers and non-carriers on measures of general cognitive ability and memory increased with age (Wisdom et al., 2011).

Due to the limitations of both linkage analysis and candidate gene studies, as well as the availability and affordability of genome-wide association studies, linkage analysis and candidate gene studies will not be further discussed in this Thesis.

1.3.2.4. Genome-wide association studies

GWAS of general cognitive ability found similar small effect estimates as discussed in Section 1.3.1.4, the largest GWAS to date by G. Davies et al. (2015a) showed that, in a sample of nearly 54,000 individuals, the most significant SNP had an effect size of 0.03 SD change in general cognitive ability per allele. The small effect sizes detected by GWAS have led to the ‘fourth law of behavioural genetics’, stating: “A typical human behavioural trait is associated with very many genetic variants, each of which accounts for a very small percentage of the behavioural variability” (Chabris et al., 2015, p. 305). Traits influenced by many genes of small effects are also called ‘polygenic traits’, as discussed in Section 1.3.1.6.

1.3.2.5. General cognitive ability

Several GWAS of general cognitive ability, as well as specific cognitive abilities, have been performed in the past ten years (Benyamin et al., 2014; G. Davies et al., 2015a; G. Davies et al., 2016b; G. Davies et al., 2011; De Jager et al., 2012; Debette et al., 2015a; Ibrahim-Verbaas et al., 2016; Kirkpatrick, McGue, Iacono, Miller, & Basu, 2014; Need et al., 2009; Okbay et al., 2016b; Rietveld et al., 2014; Trampush et al., 2017). Earlier studies were unable to detect any genome-wide significant SNPs for general cognitive ability in both childhood and adulthood in samples of 750 individuals (Need et al., 2009), 3500 individuals (G. Davies et al., 2011), 7100 individuals (Kirkpatrick et al., 2014) or 17,989 individuals (Benyamin et al., 2014), except for the GWAS by De Jager et al. (2012), who reported genome-wide significant results in the *APOE* region on chromosome 19. The *APOE* gene is a major genetic risk factor for Alzheimer’s disease (Corder et al., 1993; Genin et al., 2011), but has also been associated

with cognitive phenotypes in older age (I. J. Deary et al., 2002; Small, Rosnick, Fratiglioni, & Bäckman, 2004; Wisdom et al., 2011) and non-pathological cognitive ageing (G. Davies et al., 2014; Zhang & Pierce, 2014). Whereas GWAS of cognitive ability generally exclude individuals with dementia to ensure that all individuals are cognitively healthy, the study by De Jager et al. (2012) included 152 individuals with dementia and 151 individuals with mild cognitive impairment, meaning that just under 60% of the sample was cognitively healthy. It is therefore possible that this small GWAS picked up the APOE locus due to its association with Alzheimer's disease rather than with cognitive ability.

The first genome-wide significant hits for general cognitive ability were found on chromosome 6 (*MIR2113*), chromosome 14 (*AKAP6* and *NPAS3*), and chromosome 19 (*APOE* and *TOMM40*) in a meta-analysis of 53,949 individuals from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (G. Davies et al., 2015a). Some of the hits have previously been associated with educational attainment (*MIR2113*) (Rietveld et al., 2013), brain development (*NPAS3*) (Kamm, Pisciotto, Kliger, & Franchini, 2013; Sha et al., 2012), and cognitive ability or Alzheimer's disease (*APOE* and *TOMM40*) (G. Davies et al., 2014; Lambert et al., 2013). More recently, a smaller GWAS meta-analysis of general cognitive ability, in a sample of 35,298 individuals from the Cognitive Genomics Consortium (COGENT), identified two genome-wide significant loci on chromosome 1 (*LOC105378853*) and chromosome 2 (*CENPO*) (Trampush et al., 2017). The hit on chromosome 1 fell within a large intergenic non-coding RNA and the hit on chromosome 2 has previously been associated with height (Wood et al., 2014). Trampush et al. (2017) meta-analysed nominally significant SNPs ($p < 0.05$) from the COGENT GWAS with the suggestive SNPs ($p < 1 \times 10^{-5}$) from the CHARGE GWAS (G. Davies et al., 2015a). The findings from this meta-analysis supported the previously identified loci from the CHARGE GWAS (G. Davies et al., 2015a) on chromosome 6 and chromosome 14, and also identified a novel locus on chromosome 3. It is important to note that the COGENT study had a mean age (SD) of 45.6 (8.6) years, whereas

the CHARGE study only included individuals aged 45 years or older, this might explain the discrepancy in results between the two studies. Three loci were identified in a GWAS of general cognitive ability on 36,035 individuals on chromosome 7, chromosome 14 and chromosome 22 (G. Davies et al., 2016b). The strongest association was on chromosome 22 and involved a region that included genes involved in mitochondrial function (*NDUFA6*) (Emahazion & Brookes, 1998), drug metabolism (*CYP2D6*) (Gaedigk, Blum, Gaedigk, Eichelbaum, & Meyer, 1991), and Alzheimer's disease (*SEPT3*) (Takehashi et al., 2004). The region on chromosome 7 included the *PDE1C* gene, involved in the calcium-calmodulin complex (Repaske, Swinnen, Jin, Van Wyk, & Conti, 1992), and the region on chromosome 14 included the *FUT8* gene.

The studies discussed in this section all examined genetic contributions to cognitive ability directly; an alternative approach to identify genetic variants for cognitive ability is the proxy-phenotype method (Rietveld et al., 2014), in which a GWAS is performed to identify SNPs associated with a proxy phenotype, this is followed by a test of association between the identified SNPs ($P < 1 \times 10^{-5}$) and the phenotype of interest in an independent sample. Rietveld et al. (2014) adopted this method using educational attainment as a proxy phenotype for cognitive ability, based on the findings of previous studies showing that educational attainment is a good proxy for cognitive ability (Calvin et al., 2012; I. J. Deary & Johnson, 2010; Marioni et al., 2014b; Wainwright, Wright, Geffen, Luciano, & Martin, 2005). The first stage of the method identified 69 independent SNPs that were associated with educational attainment ($P < 1 \times 10^{-5}$), of which three were significantly associated with cognitive ability after correction for multiple testing. Each of the three SNPs was associated with ~0.02 SD increase in cognitive performance. PRS based on the 69 educational attainment SNPs explained between 0.2 and 0.4% of the variance in cognitive performance in four cohorts with a total sample size of 4463 individuals. The most recent GWAS for educational attainment found a genetic correlation of 0.75 ($SE = 0.05$) with cognitive ability, indicating that a large proportion of the phenotypic

correlation between educational attainment and cognitive ability is due to genetic factors (Okbay et al., 2016b). Based on these findings, supporting the idea that educational attainment is a good proxy for cognitive ability, this thesis will include educational attainment as a proxy measure of cognitive ability, particularly when examining the overlap between cognitive ability and health.

1.3.2.6. Specific cognitive abilities

In addition to general cognitive ability, the genetic aetiology of performance on specific measures of cognitive ability has also been analysed. Although many specific cognitive abilities exist (Tucker-Drob, 2009), only a few, including memory, executive function and processing speed, have been subject to GWAS (G. Davies et al., 2016b; Debette et al., 2015a; Ibrahim-Verbaas et al., 2016). The GWAS for memory (Debette et al., 2015a), and executive function and processing speed (Ibrahim-Verbaas et al., 2016) were performed using data from the CHARGE consortium and included 29,076 individuals for memory, 32,070 individuals for processing speed, and between 5429 and 13,454 individuals for executive function. Two genome-wide significant loci were associated with memory, one of which was in LD with the *APOE* gene, previously associated with Alzheimer's disease (Lambert et al., 2013). One genome-wide significant locus (*CADM2*) on chromosome 3 was identified for processing speed and has previously been associated with both educational attainment (G. Davies et al., 2016b) and BMI (Speliotes et al., 2010). This might indicate a shared genetic aetiology between cognitive ability and health. No genome-wide significant loci were identified for executive functioning, which could possibly be due to the relatively small samples sizes (< 14,000 individuals). A substantially larger GWAS of 112,151 individuals in UK Biobank identified two genome-wide significant loci (*SPATS2L* on chromosome 2 and *SH2B3* on chromosome 12) associated with processing speed (G. Davies et al., 2016b), *SH2B3* has

previously been associated with neurodegenerative diseases and longevity (Auburger et al., 2014). No genome-wide significant loci were identified for memory.

To sum up, individual differences in cognitive ability are partly due to genetic variation. Common genetic variants account for approximately 30 % of the variance in cognitive ability. GWAS have shown that cognitive ability is influenced by many common genetic variants (SNPs), each with a very small effect size.

1.4. Shared genetic aetiology with health

The previous Sections of this Chapter have discussed the genetic aetiology of cognitive ability and showed some associations with health outcomes. Polderman et al. (2015) and Pickrell et al. (2016) provided a comprehensive analysis of genetic contributions to a large range of health traits. The phenotypic associations between cognitive ability and health may therefore, in part, be due to a shared genetic aetiology. Understanding the genetics of cognitive ability and its overlap with the genetics of health outcomes will help elucidate common pathways of disease outcomes. This Section of the introduction will discuss the potential shared genetic aetiology between cognitive ability and health. Studies assessing the shared genetic aetiology between cognitive ability and health using a quantitative design (such as twin studies) have been relatively sparse, but the availability of genotype data has led to an increase in the investigations into the shared genetic aetiology between cognitive ability and health.

1.4.1. Mortality

The phenotypic association between cognitive ability and mortality has been well-replicated (Calvin et al., 2011) and recent studies have reported this association to be partly due to genetic factors (Arden et al., 2016; Marioni et al., 2016a). A behavioural genetics meta-analysis including 1312 twin pairs from America, Sweden and Denmark, showed that the genetic

contribution to the small phenotypic correlation between cognitive ability and mortality was 95% (Arden et al., 2016). This finding was supported by a study of over 130,000 individuals examining the association between PRS for educational attainment (a proxy for cognitive ability) and parental longevity, which showed that a 1 SD increase in PRS for educational attainment was associated with ~2.5% lower risk of parental mortality (Marioni et al., 2016a).

1.4.2. Physical health

Wraw et al. (2015) showed a phenotypic association between childhood cognitive ability and better physical health at age 50. A recent study (Harris et al., 2016a) examined the genetic overlap between self-rated health, a powerful predictor of future health, and among other traits, cognitive ability. They showed a genetic correlation, using LDSR, of 0.4 (SE = 0.05) and 0.6 (SE = 0.03) with cognitive ability and educational attainment, respectively. PRS analysis indicated that polygenic profiles for general cognitive ability explained 0.12 % ($p = 1.29 \times 10^{-30}$) of the variance in self-rated health. These results indicate that the same generic variants possibly influence both cognitive ability and self-rated health.

When assessing more specific health outcomes, similar results have been reported. Luciano et al. (2010) showed, in an extended behavioural genetic pedigree based study of 6118 individuals from 1983 families, that the association between behavioural risk factors for cardiovascular disease, such as physical activity, psychological distress, and lung capacity, and cognitive ability is largely due to genes (30 – 94 %). Using a PRS approach, Hagenaars et al. (2016a) examined the association between coronary artery disease polygenic risk and cognitive ability in 11,387 older adults and found that a higher genetic risk for coronary artery disease was associated with lower general cognitive ability, verbal intelligence and memory performance. This finding was supported by a study performing LDSR on a large range of health outcomes, who reported a negative genetic correlation between coronary artery

disease and educational attainment ($r_g = -0.28$, $SE = 0.07$) (Brendan K. Bulik-Sullivan et al., 2015a), but did not find a significant genetic correlation between childhood cognitive ability and coronary artery disease.

With regards to cardiovascular risk factors such as stroke, type 2 diabetes and BMI, several studies have shown a shared genetic aetiology between these risk factors and cognitive ability (Brendan K. Bulik-Sullivan et al., 2015a; Harris et al., 2016b; Luciano et al., 2014; Marioni et al., 2016b). Harris et al. (2016b) found a negative correlation between polygenic risk for stroke and general cognitive ability ($r = -0.07$), indicating that individuals with a higher genetic risk for stroke have poorer cognitive performance. Marioni et al. (2016b) reported that, in a sample of 6815 unrelated individuals, polygenic profile scores for general cognitive ability explained 0.08 % of the variance in BMI, while polygenic profile scores for BMI explained 0.42 % of the variance in cognitive ability. A smaller study including 3152 individuals did not support these findings (Krapohl et al., 2016), the discrepancy in results is likely due to the difference in sample size between the two studies. Marioni et al. (2016b) also showed a moderate genetic correlation between general cognitive ability and BMI (r_g between -0.10 and -0.51), using both LDSR and a bivariate GCTA-GREML study. Both BMI and different classes of obesity have been found to be genetically correlated with childhood cognitive ability and educational attainment (r_g between -0.17 and -0.29) using LDSR (Brendan K. Bulik-Sullivan et al., 2015a). Similar to its inconsistent phenotypic association, as discussed in Section 1.2.2.2, the shared genetic aetiology between cognitive ability and type 2 diabetes is less clear. Whereas Luciano et al. (2014) reported a counterintuitive positive association between polygenic risk for type 2 diabetes and cognitive ability, two studies using a small number of SNPs to create a polygenic risk score for type 2 diabetes did not find an association with cognitive ability (Bonilla et al., 2012; De Jager et al., 2012). Brendan K. Bulik-Sullivan et al. (2015a) reported no significant genetic correlation between childhood cognitive ability and measures of type 2 diabetes (including HbA1c, glucose and insulin measures), but did report significant negative genetic

correlations between educational attainment and measures of type 2 diabetes (r_g between -0.11 and -0.30).

1.4.3. Mental health

This Section will focus on the shared genetic aetiology between cognitive ability and mental health (Brendan K. Bulik-Sullivan et al., 2015a; Clarke et al., 2016; Georgiades et al., 2016; Harris et al., 2014; Hill et al., 2016; Kendler, Ohlsson, Sundquist, & Sundquist, 2015; Krapohl et al., 2016; Kuntsi et al., 2004; McIntosh et al., 2013; Touloupoulou et al., 2007). In a behavioural genetic study of 267 twins a genetic correlation of -0.61 (95% CI -0.71 to -0.48) was found between general cognitive ability and schizophrenia, 92% of the phenotypic variation between the two traits was due to genes (Touloupoulou et al., 2007). This was supported by Kendler et al. (2015) who, using a behavioural genetic study, showed that high general cognitive ability attenuated the influence of genetic risk for schizophrenia, as well as by Hill et al. (2016), who reported a genetic correlation, using the molecular genetic method LDSR, of -0.23 (SE = 0.03). A shared genetic aetiology between general cognitive ability and schizophrenia was also indicated using the PRS approach in a sample of 937 individuals, where genetic risk for schizophrenia explained between 0.6 and 0.8% of the variance in general cognitive ability (McIntosh et al., 2013). Hill et al. (2016) also found, using LDSR, significant genetic correlations between childhood cognitive ability and Alzheimer's disease (r_g = -0.34, SE = 0.11), and autism (r_g = 0.36, SE = 0.11), between general cognitive ability and Alzheimer's disease (r_g = -0.32, SE = 0.08), and between educational attainment and bipolar disorder (r_g = 0.26, SE = 0.06), autism (r_g = 0.32, SE = 0.07), and Alzheimer's disease (r_g = -0.32, SE = 0.07). The positive genetic correlation between cognitive ability, in both childhood and adulthood, and autism, has been also been reported using the PRS approach by Clarke et al. (2016) in a meta-analysis of 15,885 individuals. Harris et al. (2014) did not report a significant association between polygenic risk for Alzheimer's disease and cognitive ability in

a sample of 3500 individuals, however this polygenic risk score was based on a GWAS of Alzheimer's disease that only included 3,941 Alzheimer's disease cases and 7,848 controls. A more recent GWAS has been released including 17,008 Alzheimer's disease cases and 37,154 controls (Lambert et al., 2013).

Twin and family studies have shown that the phenotypic association between cognitive ability and health is partly due to genes, and using molecular genetic methods such as LDSR and PRS it has been shown that some of the same genes are associated with both cognitive ability and health. Several studies discussed in this Section lack power due to small sample sizes, particularly the PRS studies. It is therefore of high importance to attempt to replicate and extend these findings in large samples to be able to further dissect the shared genetic aetiology between cognitive ability and health.

1.5. Summary

This Chapter provided an introduction to one of the key fields reported in this thesis; cognitive ability, phenotypic and genetic associations of cognitive ability with health, and relevant genetics concepts, methods and results. The empirical work in this thesis focussed on cognitive ability will address the key question:

- 1) Do cognitive ability and health have some shared genetic aetiology?

Empirical evidence for this question will be provided in Chapters 4 and 5, relating to: shared genetic aetiology of cognitive ability with mental and physical health in UK Biobank; and the genetic aetiology of executive function and its shared genetic aetiology with general cognitive ability. The next Chapter will provide a comprehensive introduction to the association between negative emotions and health.

2. Negative emotions

2.1. Unfolding the relation between emotions and disease

Today's science is in the process of understanding the relationship between emotions and health. Long before modern science started, philosophers and physicians already acknowledged an association between the way people feel (their mental health) and their physical health. One of the personality traits that is of great importance to public health is neuroticism, which is characterized by the tendency to experience negative emotions. Neuroticism is important to the public health, because it has been associated with a range of mental and physical health outcomes. These associations might contribute to the understanding of health inequalities in the population and this part of the introduction will therefore focus on the personality trait of neuroticism. First, a brief historical context will be presented on the different theories of personality, starting with Hippocrates' and Galen's theory of the four bodily humours and ending with Costa and McCrae's Five Factor Model of personality. This will be followed by a brief discussion of the stability of the personality trait of neuroticism. Third, empirical work examining the association between neuroticism and health outcomes will be presented in the following order: cardiovascular disease, cardiovascular disease risk factors, mental health, and fatigue. The final part of this Section will discuss one of the proposed mechanisms underlying the associations between neuroticism and health; a shared genetic aetiology.

2.2. A brief history

2.2.1. The four bodily humours

In the ancient Greek times, Hippocrates (460 – 370 BC) hypothesized that the four bodily fluids, blood, yellow bile, black bile, and phlegm, are the basis of human health. He proposed

that these four fluids, also called humours, produce perfect health when balanced. If unbalanced, for example, because of an excess of one of the fluids, it could lead to diseases and disabilities (Chadwick, 1983). Galen (130 – ~216 AD), a well-known philosopher and physician, continued the work five hundred years after Hippocrates and added the idea of temperament to the theory of bodily humours. Similar to Hippocrates, Galen hypothesized that excess of one of the bodily humours would not only lead to physical illness, but also to a certain type of personality. In Galen's work '*De Temperamentis*', he suggests that the four main personality types are sanguine, choleric, melancholic, and phlegmatic (Allport, 1961). The sanguine personality type is based on the humour of blood, with the heart being its main organ. People with this temperament tend to be lively, optimistic and carefree. An excess of yellow bile is associated with the choleric temperament, with the liver and gall bladder being its main organs. These people tend to be egocentric, analytical and passionate. The melancholic temperament is associated with an excess of black bile and the tendency of a lonely, introverted, and depressed personality. The main organ of this temperament is the spleen. The fourth temperament, phlegmatic, is associated with an excess of phlegm and forms the calm, reasonable and apathetic character. The brain is its main organ, which could reflect the lack of emotions in this temperament. Figure 2-1 displays the four bodily humours and the main personality types.

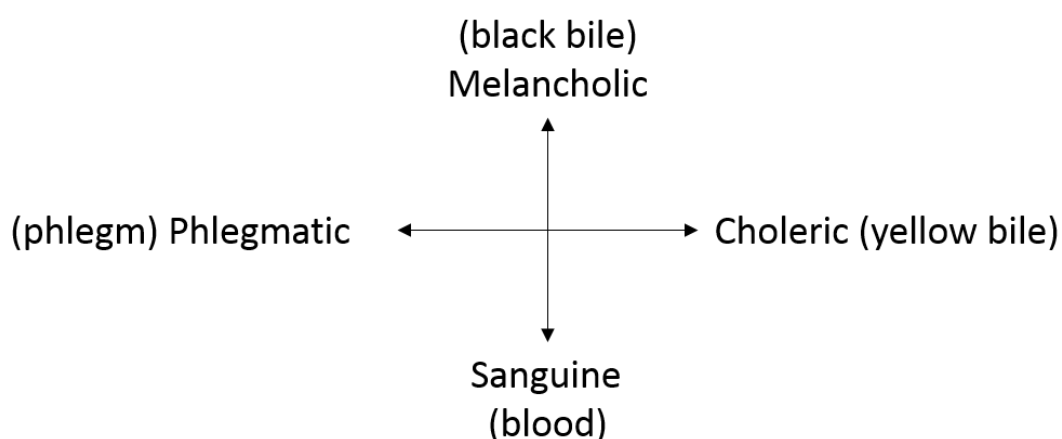


Figure 2-1. Hippocrates and Galen's theory of the four bodily humours.

The theory of the four bodily humours remained popular during the Renaissance, as shown in Burton's 'The Anatomy of Melancholy' (Burton, 1621). The theory, however, was already in jeopardy during the time Burton wrote his book. Galen based his theory on anatomical assumptions, but he had never dissected a human body. His assumptions started to receive criticism in the 16th century due to the advances in anatomy by for example Andreas Vesalius. Vesalius's book 'De Humani Corporis Fabrica' exposed a large range of mistakes in Galen's anatomical assumptions. Due to the emergence of these new findings and the development of new medical techniques, emotions became more separate from diseases. This led to the theory being rejected due to the lack of empirical support and it now only exists as a descriptive metaphor.

2.2.2. Psychosomatic medicine

The development of psychosomatic medicine expanded the theory that an individual's personality could have an effect on the development of disease. Helen Flanders Dunbar (1943) suggested that different personality profiles were associated with different diseases. One example is the cardiac type of personality, which represents relentlessly ambitious and aggressive males with a tendency towards depression, that was associated with the development of coronary insufficiency. Dunbar acknowledged that many individuals who have traits that are part of Dunbar's personality profiles, such as the cardiac type, are free of any illness. She argued that the diagnostic value of her personality profiles would be in the co-occurrence of traits, meaning that one trait will likely not lead to cardiovascular disease, but multiple traits together might. Franz Alexander (1950) focussed more on the emotional states and adjustments to the environment instead of the more superficial personality types suggested by Dunbar. He stated that "the true correlation may not be between personality make-up and coronary disease, but between the mode of living and disease" (Alexander, 1950, p. 73). Disturbance of the personality make-up, for example by mode of living, could lead to

disturbance of a bodily organ, which is somewhat similar to the theory of the four humours described in an earlier part of this Chapter. Asthma would, for example, be linked to an unconscious desire to be protected by a mother, also named separation anxiety, while ulcers would be caused by the unconscious desire to have infantile needs satisfied. Following this idea, Alexander (1950) and Dunbar (1943) identified the Holy Seven Psychosomatic Diseases, which included bronchial asthma, hypertension, thyrotoxicosis, peptic ulcer, neurodermatitis, bronchial asthma and rheumatoid arthritis. The discovery of the *Helicobacter pylori* bacteria by Marshall and Warren (1984) was one of the findings that contributed to the theory of the psychosomatic illnesses being abandoned, as this bacterium was found to be an important factor in the development of ulcers. It is important to note, though, that the presence of the *Helicobacter pylori* bacteria does not necessarily lead to ulcers. Individuals differ in the way they experience symptoms and in the effects of stress on the body. Instead of ulcers being caused purely by psychosomatic factors, it is more likely that interplay of both psychosocial and physical factors could lead to the development of ulcers.

2.2.3. Friedman & Rosenman: The A, B, and C personality types

Two cardiologists, Meyer Friedman and Ray Rosenman, further explored the relationship between cardiovascular disease and personality in the 1950s. In their paper (Friedman & Rosenman, 1959), they selected three groups of males according to three specific overt behaviour patterns. The first pattern, Type A, was characterised by a drive for achievement, sense of urgency and an eagerness to compete. Type B, the second pattern, was the opposite of Type A and characterised by a lack of ambition, competitiveness, and drive. The third behaviour pattern, Type C, was very similar to Type B, but also included a chronic state of anxiety. Friedman and Rosenman examined if there was an association between the three types of behaviour and measures of cardiovascular disease, which included clotting time, serum cholesterol and clinical diagnoses of cardiovascular disease, diagnosed using an

electrocardiogram. All males in the study were aged between 30 and 60 years. They found that males in the Type A group had significantly higher cholesterol levels (253 mg/100 ml) compared to males in the Type B group (215 mg/100 ml) and the Type C group (220 mg/100 ml). Fully developed, showing a complete behavioural pattern, Type A males had a significantly faster clotting time (6.8 minutes) compared to fully developed males in the Type B (7.2 minutes) or Type C (7.4 minutes) groups. Similarly, 28% of males in the Type A group showed signs of cardiovascular disease, while only 4% of males in the Type B and C group showed signs of cardiovascular disease. These results did not attenuate when adjusting for confounding factors such as diet, alcohol intake, smoking or exercise. Similar to Dunbar, Friedman and Rosenman concluded that males with Type A personality were prone to cardiovascular disease. While these studies did show an association between type A personality and cardiovascular disease, later studies have failed to replicate these findings (Gallacher, Sweetnam, Yarnell, Elwood, & Stansfeld, 2003; Myrtek, 2001; Ragland & Brand, 1988; Šmigelskas, Žemaitienė, Julkunen, & Kauhanen, 2015). A large meta-analysis (Myrtek, 2001), including over 74,000 individuals, reported a correlation of 0.003 and concluded that the effect of the association between type A personality and cardiovascular mortality is negligible. A more recent study (Šmigelskas et al., 2015) supported these findings and showed inconsistent results between different measures of type A personality and cardiovascular mortality, some measures showed a decreased risk, while others showed an increased risk of cardiovascular mortality. The authors conclude that there is no clear association between type A personality and cardiovascular mortality, and if there were to be an association this would likely be due to sample and study specific factors.

2.3. Trait theories

The next Section of this Chapter will discuss trait theories of personality. According to these trait theories, personality is formed by the combination and interaction of different traits. The

personality trait theories have two important underlying assumptions; traits are stable over time, and traits directly influence behaviour (Matthews, Deary, & Whiteman, 2009).

2.3.1. Eysenck's three-factor theory

A biological theory of personality was developed by H. J. Eysenck (1967), he used factor analysis (H. J. Eysenck, 1947), to identify two personality factors; extraversion and neuroticism. Extraversion is characterised by the tendency to enjoy positive events, while neuroticism is characterised by the tendency to experience negative emotions. Later Eysenck added a third trait to his model, psychoticism. Individuals who score high on this trait are characterised by “cold, impersonal, lacking in sympathy, unfriendly, untrustful, odd, unemotional, unhelpful, antisocial, lacking in insight, strange, with paranoid ideas that people were against him” (H. J. Eysenck & Eysenck, 1976, p. 47).

Eysenck hypothesised that the individual differences in personality are caused by biological factors, specifically by differences in the levels of arousal of two brain systems, i.e. the reticulo-cortical and the reticulo-limbic system (H. J. Eysenck, 1967; H. J. Eysenck & Eysenck, 1985). The reticulo-cortical system determines the levels of emotion, motivation and conditioning, depending on the arousal of the cerebral cortex. Eysenck argued that changes in this system are associated with individual differences in extraversion, while changes in the reticulo-limbic system are associated with individual differences in neuroticism. The arousal of the reticulo-limbic system could lead to the experience of intense emotions, such as anxiety. Eysenck suggested that the dopamine neurotransmitter, responsible for the regulation and experience of emotions, might cause individuals differences in psychoticism. Eysenck's theory has greatly influenced the study of individual differences, but due to, among other things, its biological complexity, the theory has not been able to withstand the scientific empirical examinations (M. W. Eysenck, 2016; Matthews, 2016).

2.3.2. Five-factor model

While Eysenck's three-factor model focussed on the broad personality traits, Raymond Cattell focussed on narrower, supposedly underlying traits. His work was based on Allport and Odbert's list of English trait names (Allport & Odbert, 1936). They found over 19,000 words to describe psychological aspects of differences in individuals. Cattell argued that different words often describe the same trait, he reduced this list to 4500 words and identified 16 so-called primary personality factors (Cattell, 1943a, 1946). These 16 factors can be reduced to fewer broader dimensions, i.e. extraversion, anxiety/neuroticism, tough poise, independence, and control, with the first two lining up with Eysenck's extraversion and neuroticism personality factors (Krug & Johns, 1986). The main criticism of Cattell's theory is that is too complex and a total of five factors can be used to describe much of personality variation (Fiske, 1949; Norman, 1963).

The most-used model of personality today is the five-factor model, first developed by Tupes and Christal (1961) and followed up by Norman (1963). This model is, as is Cattell's sixteen personality factor model, based on the lexical hypothesis. Tupes and Christal (1961) showed five factors that underlie the personality structure, based on eight different samples, which also included Cattell's original samples. They named the personality factors surgency/extroversion, agreeableness, dependability, emotional stability, and culture. A later study by Norman (1963) showed similar results, but he renamed the dependability factor to conscientiousness. The most commonly used names for the five personality factors, as proposed by Costa and McCrae (1992), are neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Costa and McCrae (1976) first identified the factors of neuroticism and extraversion based on cluster analysis of Cattell's 16 personality factors, as well as a third factor that, after adding more items to the analysis, was named openness to experience (Costa

& McCrae, 1978). They decided that each factor should be represented by six behavioural traits, called facets, as shown in Table 2-1. Later they also added the factors of agreeableness and conscientiousness, which completed the five factor model. The factors of neuroticism and extraversion were based on the personality model of Cattell, but they can be traced back even further, particularly neuroticism, to 1925, where it has been used in different personality scales (I. J. Deary & Bedford, 2011; Guilford & Guilford, 1939; Laird, 1925; Thurstone & Thurstone, 1930). Neuroticism can be described as the tendency to experience negative emotions, with at the high end of the dimension, a greater likelihood of experiencing feelings of anxiety and depression, and on the low-end emotional stability. The dimension of extraversion describes the experience of sociability and impulsiveness on the high end, whilst the low end, also called introversion, is characterised by shy and quiet behaviour. The third dimension, openness to experience, is the tendency to engage in intellectual activities and new experiences on the high end, in contrast to conservative behaviour on the low end. Agreeableness is characterised by trusting and compliant behaviour on the high end of the dimension, versus stubbornness and independence on the low end. The high end of the final dimension of the five-factor model, conscientiousness, is characterised by being well-organized and responsible, compared to the low end, which is characterised by a tendency to be disorganised and careless. Table 2-1 shows the five personality traits according to the Five Factor model and their associated trait facets.

Table 2-1. Trait facets associated with five personality traits as proposed by Costa and McCrae's Five Factor model

Trait	Trait facets
Openness to experience	Fantasy, aesthetics, feelings, actions, ideas, values
Conscientiousness	Competence, order, dutifulness, achievement striving, self-discipline, deliberation
Extraversion	Warmth, gregarious, assertive, activity, excitement seeking, positive emotion
Agreeableness	Trust, straightforward, altruism, compliant, modesty, tenderminded
Neuroticism	Anxiety, angry hostility, depression, self-conscious, impulsive, vulnerable

2.4. Stability, age and sex differences

Many studies have examined the longitudinal stability of neuroticism, and have shown that its stability increases with age (B. W. Roberts & Delvecchio, 2000). However, mean neuroticism scores increase from adolescence into adulthood, peaking in late adolescence, and show a steady decline through midlife (Donnellan & Lucas, 2008; Lucas & Donnellan, 2009; B. W. Roberts & Mroczek, 2008; Soto, John, Gosling, & Potter, 2011; Terracciano, McCrae, Brant, & Costa, 2005). Figure 2-2 shows the age and sex distribution of neuroticism scores in a study of approximately 1.2 million individuals aged between 10 and 60 years (Soto et al., 2011). Soto et al. (2011) used *T*-scores to quantify the differences between males and females, which are standardized scores with a mean of 50 and a SD of 10. A 5 *T*-score point difference between males and females was found in mid-adolescence, which indicates a medium effect based on Cohen's guidelines for interpreting effect sizes (J. Cohen, 1988). This effect attenuated to a 2 *T*-score point difference, a small effect, in later life. Females have consistently been reported to score higher on neuroticism than males (Costa, Terracciano, & McCrae, 2001; Soto et al., 2011), which is in line with the idea that females are diagnosed more often with disorders related to negative emotions, such as major depressive disorder, anxiety disorder, and panic disorder (N. R. Eaton et al., 2012). Costa et al. (2001) showed that sex differences in

neuroticism are strongest in European and American cultures, with differences in z-scores between males and females ranging from 0.42 to 0.75, and weakest in Asian and African cultures where the z-scores ranged from -0.02 to 0.40. They argued that the differences in neuroticism are seen in all cultures, but that these differences could be attributed to gender roles instead of personality traits in traditional cultures, such as the African and Asian cultures.

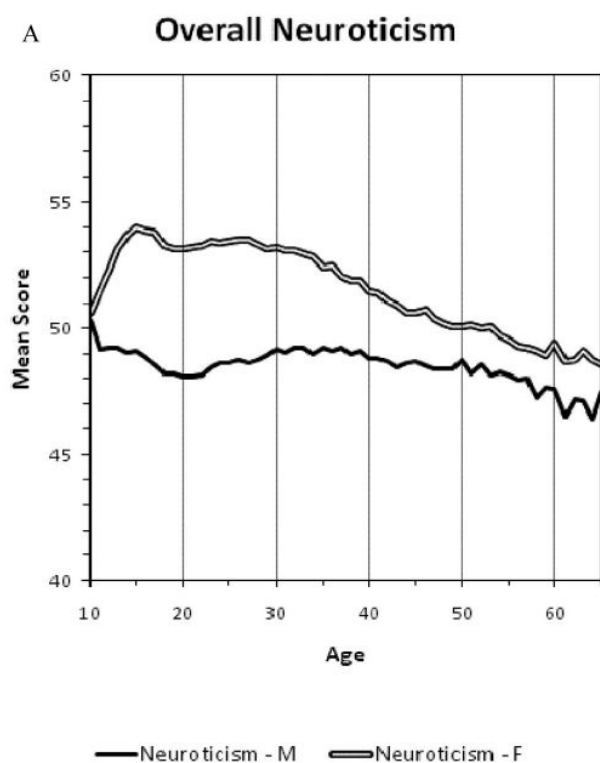


Figure 2-2. Means for overall Neuroticism by age and gender, based on *T*-scores with a mean of 50 and a SD of 10. Single lines show the means for males, and double lines show the means for females. Reprinted with permission from Soto et al. (2011). Copyright 2011 by American Psychological Association.

One of the key assumptions of personality trait theories is that personality traits directly influence behaviour (G. Matthews et al., 2009). It is therefore conceivable that personality traits are associated with morbidity and mortality. As mentioned earlier, due to the public health significance of neuroticism, the main aim of this part of the Thesis is the association between negative emotions, specifically neuroticism, and health; therefore, the next part of

this Thesis will provide an overview of the associations between the personality trait of neuroticism and health, and discuss potential mechanisms underlying these associations.

2.5. Negative emotions and health

2.5.1. Cardiovascular disease

Negative emotions and health have been linked together since Hippocrates and Galen's theory of the four bodily humours; one of the most studied associations between personality and health is the association with cardiovascular disease. Multiple studies have examined the association between negative emotions (including anger, anxiety, and depression) and cardiovascular disease, and found consistent evidence between higher levels of negative emotions and a higher risk of cardiovascular disease (Booth-Kewley & Friedman, 1987; Kubzansky & Kawachi, 2000). When focussing on the more specific personality trait of neuroticism, similar results were found, but with an important distinction. Paul Costa (1987) for example, examined the association between neuroticism, angina and coronary artery disease, in a sample of approximately 7000 individuals who had received a detailed medical examination as part of the National Health and Nutrition Examination Survey (NHANES1) Epidemiologic Follow-up Study. He found that individuals who reported more chest pain had higher levels of neuroticism, but he did not find an association between increased mortality due to myocardial infarction and neuroticism levels. Similar results were found by Watson and Pennebaker (1989), who showed consistent correlations between higher levels of neuroticism and more health complaints, but no association with coronary artery diseases, and suggested neuroticism to be "a more general trait of somatopsychic distress" (Watson & Pennebaker, 1989, p. 248). More recent studies have, however, shown associations between neuroticism and cardiovascular disease (Jokela, Pulkki-Råback, Elovainio, & Kivimäki, 2014b; Shipley, Weiss, Der, Taylor, & Deary, 2007). For example, Jokela et al. (2014b) found, in an individual-participant meta-analysis of just under 25,000 individuals, that higher neuroticism was

associated with coronary artery disease mortality, 1 SD change in neuroticism was associated with a 16% risk increase for coronary artery disease mortality (HR 1.16, 95% CI = 1.04 – 1.29). They suggested that neuroticism and coronary artery disease might be linked via physiological pathways, for example by activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, which has been linked to risk factors for cardiovascular disease, including the metabolic syndrome, decreased heart rate variability, and atherosclerosis. Čukić and Bates (2015) showed that higher neuroticism was associated with decreased heart rate variability, which was independent of cardiovascular disease diagnosis. This supports the hypothesis that neuroticism and cardiovascular disease might be linked via physiological pathways.

2.5.2. Cardiovascular risk factors

2.5.2.1. Type 2 diabetes

Type 2 diabetes, obesity, hypertension, and smoking are major risk factors for cardiovascular disease and have also been linked to neuroticism. Personality traits could play an important role in the development of type 2 diabetes, but the results for an association between neuroticism and type 2 diabetes have been inconsistent. Goodwin, Cox, and Clara (2006) found an association between higher levels of neuroticism (1 SD above the mean) and increased likelihood of diabetes in a sample of around 6000 individuals, which remained significant after adjusting for both sociodemographic factors and psychiatric disorders. Individuals with high neuroticism had a three times higher risk of a diabetes diagnosis (OR = 3.00, 95% CI = 1.62 – 5.58), when the model was unadjusted. After adjusting for sociodemographic factors and psychiatric disorders, this increased to a 3.33 times higher risk for diabetes diagnosis (OR = 3.33, 95% CI = 1.57 – 7.04). In the same year, another study was published by Goodwin and Friedman (2006), which examined the association between neuroticism and diabetes in the Midlife Development in the United States (MIDUS) survey,

including a total of 3032 individuals. This study did not find any association between diabetes and neuroticism. It is important to note that in both studies the type of diabetes was not specified and diabetes diagnosis was based on self-report. A pooled analysis of five cohort studies, including 34,913 diabetes-free individuals (Jokela et al., 2014a), did not provide consistent evidence for an association between self-reported diabetes and neuroticism; only one of five cohorts showed that higher neuroticism was associated with diabetes diagnosis. More recently, Čukić, Möttus, Realo, and Allik (2016) examined the association between diabetes, measured using a combination of self-report and medical records confirming diagnosis, and neuroticism, measured by both self-report based ratings and informant-based ratings. Significant associations were found between higher levels of neuroticism and diagnosis of diabetes using the self-report based personality ratings (OR = 1.20, 95% CI = 1.01 – 1.42), but not when using the informant based personality ratings (OR = 1.13, 95% CI = 0.95 – 1.35). Eriksson et al. (2008) examined the association between psychological distress and type 2 diabetes. Psychological distress was measured by a Likert-scale questionnaire asking about the prevalence of symptoms of fatigue, anxiety, apathy, insomnia, and depression in the past year. The answers were summed and divided in quartiles, the two median quartiles were combined leading to three different groups of psychological distress (low, middle, and high). The results showed that high psychological distress was associated with both pre-diabetes (OR = 1.90, 95% CI = 1.20 – 2.80) and type 2 diabetes (OR = 2.20, 95% CI = 1.20 – 4.10) in males, and middle psychological distress with pre-diabetes only (OR = 1.80, 95% CI = 1.10 – 3.00) in females, after adjusting for age, BMI, family history of diabetes, smoking status, physical activity and socio-economic status. Pre-diabetes was defined as impaired fasting glucose and impaired glucose tolerance using an oral glucose tolerance test. In males, symptoms of fatigue were on its own also associated with both pre-diabetes and type 2 diabetes (OR = 1.80, 95% CI = 1.10 – 2.90). A study of just under a 1000 non-diabetic individuals found that neuroticism interacts with BMI to predict both insulin levels and insulin resistance (Tsenkova, Carr, Coe, & Ryff, 2012). This indicates that psychological distress, acting

together with BMI, could have an effect on the progression to disease. While some of the studies discussed in this Section did report an association between neuroticism and diabetes, others did not find such an association.

2.5.2.2. BMI

A second major risk factor for cardiovascular disease is obesity, and a growing body of evidence is showing an association between neuroticism and body weight (Armon, Melamed, Shirom, Shapira, & Berliner, 2013; Gerlach, Herpertz, & Loeber, 2015; Magee & Heaven, 2011; Sutin & Terracciano, 2016). Magee and Heaven (2011) examined this association in about 5200 Australian individuals and found that neuroticism was positively correlated with BMI. Regression models showed that neuroticism and obesity were positively associated ($OR = 1.13$, 95% $CI = 1.03 - 1.24$). They did not find an association between neuroticism and changes in body weight over a two-year period. A large cross-sectional individual-participant meta-analysis of 78,931 individuals did show an association between neuroticism and BMI in the European and Australian cohorts, but not in the American cohorts (Jokela et al., 2013). The overall association was non-significant. Armon et al. (2013) found significant associations between neuroticism and three measures of body weight, i.e. BMI ($\beta = 0.05$), waist-hip ratio ($\beta = 0.05$), and waist circumference ($\beta = 0.06$), at baseline. They also found an association between neuroticism and weight increase over a four-year period, one that was stronger in females compared to males. In females, all three measures showed a significant association between neuroticism and weight increase, with β 's between 0.06 – 0.12. In males, only change in waist-hip ratio showed a significant association with neuroticism, with a β of 0.06. This finding could explain some of the inconsistencies of the associations between neuroticism and body weight. Several studies have indicated that the effects of the association between neuroticism and body weight could be moderated by gender. Faith, Flint, Fairburn, Goodwin, and Allison (2001) showed that increased neuroticism was associated with increased BMI in

females only ($\beta = 0.08$). These results were supported by the University of North Carolina Alumni Heart Study (UNCAHS), which showed positive correlations between neuroticism and BMI in females, but not in males (Brummett et al., 2006). Females in the upper half of the neuroticism distribution weighed approximately 5 kg (1.9 kg/m^2) more than females in the lower half of the neuroticism distribution. Brummett et al. (2006) suggested that the greater stigma of obesity could be causing the sex differences, with higher levels of neuroticism leading to poorer health choices, such as overeating and physical inactivity. This is supported by Sutin and Terracciano (2016) who suggest that higher levels of neuroticism in females might lead to emotional eating that contributes to excess weight. Taken together, all these studies show that higher neuroticism is associated with higher BMI.

2.5.2.3. Blood pressure

Hypertension is a third major risk factor for cardiovascular disease, and multiple studies have examined the association of hypertension with neuroticism (Cheng, Montgomery, Treglown, & Furnham, 2016; Goodwin et al., 2006; Turiano et al., 2012). Goodwin et al. (2006) used data from the National Comorbidity Survey and showed a positive association between individuals with high neuroticism levels and self-reported hypertension status. This association remained significant after adjusting for sociodemographic measures, including age, sex, socio-economic status, race and marital status, after adjusting for psychiatric disorders the association became non-significant. This was supported by Turiano et al. (2012) who examined the association between neuroticism and self-reported blood pressure, which was measured by asking participants if their blood pressure was low, normal, slightly raised or high at their last doctor's visit. They found that higher neuroticism levels predicted higher blood pressure status ($\beta = 0.05$). Results from the National Child Development Study also showed positive associations between neuroticism and self-reported hypertension status, 1 SD increase in neuroticism was associated with a 15 % higher risk of hypertension (OR = 1.15,

95% CI = 1.09 – 1.23) (Cheng et al., 2016). It is important to note that the three previously discussed studies used self-report measures for blood pressure and hypertension, which could cause a bias towards the null hypothesis, due to misclassification of the diagnosis (Tenkorang, Sedziafa, Sano, Kuuire, & Banchani, 2015). Bibbey, Carroll, Roseboom, Phillips, and de Rooij (2013) measured blood pressure at baseline and after three acute psychological stress tasks, to examine the association between neuroticism and blood pressure stress reactivity. Blood pressure stress reactivity was defined as the difference between blood pressure after the stress tasks and blood pressure at baseline. The results showed that higher neuroticism was associated with lower blood pressure stress reactivity (β between -0.12 and -0.16). This supports the findings using the self-report measures of blood pressure and hypertension, indicating that higher neuroticism is associated with higher blood pressure. Overall, studies using both self-reported measures and physical measures indicate a positive association between neuroticism and blood pressure.

2.5.2.4. Smoking

The final cardiovascular risk factor to be discussed in this Section is smoking. The harmful effects of smoking are well known and previous research has identified multiple psychological and social risk factors for smoking, including individual differences in neuroticism (Hakulinen et al., 2015b; Munafò, Zetteler, & Clark, 2007; Terracciano & Costa, 2004; Zvolensky, Taha, Bono, & Goodwin, 2015). A study of 1638 individuals, who were part of the Baltimore Longitudinal Study on Aging (BLSA), found that current smokers had higher levels of neuroticism than individuals who had never smoked ($F(2,1635) = 17.77$) (Terracciano & Costa, 2004). This finding has been replicated by both longitudinal and cross-sectional studies. A meta-analysis of 25 studies including over 47,000 individuals reported that increased neuroticism was associated with an increased likelihood of being a smoker compared to not smoking (Cohen's $d = 0.12$, 95% CI = 0.04 – 0.20) (Munafò et al., 2007). Zvolensky et al.

(2015) examined the association between neuroticism and different smoking outcomes over a period of 10 years in a sample of 2101 individuals from the MIDUS survey. They found an association between neuroticism and lifetime cigarette use (OR = 1.20, 95% CI = 1.10 – 1.40), progression to daily smoking (OR = 1.30, 95% CI = 1.10 – 1.50), and persistence of daily smoking (OR = 1.30, 95% CI = 1.10 – 1.60). The most recent and largest study to date examining the association between smoking and neuroticism was a cross-sectional and longitudinal individual-participant meta-analysis including 79,757 individuals with a mean follow-up time of 5.2 years (Hakulinen et al., 2015b). Using the cross-sectional data, the study showed that higher neuroticism was associated with higher risk of smoking (OR = 1.19, 95% CI = 1.13 – 1.26) and an increased likelihood of being an ex-smoker (OR = 1.13, 95% CI = 1.07 – 1.19). Longitudinal analyses indicated that higher neuroticism was associated with higher odds of smoking relapse among ex-smokers (OR = 1.16, 95% CI = 1.04 – 1.30) as well as lower odds of quitting smoking among baseline smokers (OR = 0.91, 95% CI = 0.87 – 0.96). The authors suggest that smoking might be a strategy to reduce tension and anxiety among individuals with high neuroticism (Hakulinen et al., 2015b). While the effects in the above discussed studies might be relatively small, the consistently reported association between neuroticism and smoking is of great importance, due to the large number of people that smoke (Orchard, 2016). These findings highlight the importance of neuroticism in smoking behaviour and may help to enhance knowledge about smoking behaviour and improve smoking prevention and cessation programs.

2.5.3. Mental health

There is strong evidence that neuroticism and different mental disorders are associated across the lifespan. A meta-analysis, including 33 studies, showed strong associations between neuroticism and different mental disorders (Malouff, Thorsteinsson, & Schutte, 2005). The strongest association was found between neuroticism and mood disorders, with a Cohen's d

of 1.54. These results were supported by a larger meta-analysis, including 175 studies, showing that mood disorders, anxiety disorders, and substance use disorders were all characterized by high neuroticism levels (Kotov, Gamez, Schmidt, & Watson, 2010). The meta-analysis by Malouff et al. (2005) found that the strongest association was between neuroticism and mood disorders in general (Cohen's $d = 1.54$, 95% CI = 1.21 – 1.86), whilst Kotov et al. (2010) showed stronger effects for the association between neuroticism and dysthymia (Cohen's $d = 1.93$, 80% credibility interval = 1.01 – 2.84), compared to the association between neuroticism and major depressive disorder (Cohen's $d = 1.33$, 80% credibility interval = 0.44 – 2.23). Dysthymia is a chronic form of depression, while major depressive disorder could include individuals who have only been diagnosed with a single episode of depression (W. W. Eaton et al., 2008). The finding that the association with a more chronic form of depression is stronger than major depressive disorder, could implicate that the chronic nature of a disorder is associated with the extremity of neuroticism levels.

Elovainio et al. (2015) examined the longitudinal association between negative affect, as measured by the Emotionality-Activity-Sociability (EAS) Temperament Survey, and depressive symptoms in a sample of 1739 individuals who were part of the Cardiovascular Risk in Young Finns Study with a follow-up time of 15 years. The negative affect part of the EAS has been shown to be highly similar to the personality trait of neuroticism (Braithwaite, Duncan-Jones, Bosly-Craft, & Goodchild, 1984). Negative affect at baseline significantly predicted depressive symptoms at follow-up ($\beta = 0.34$, 95% CI = 0.29 – 0.40). However, this effect was attenuated to 0.04 (95% CI = -0.03 – 0.10) after adjusting for depressive symptoms at baseline. Baseline depressive symptoms were also predictive of negative affect at follow-up ($\beta = 0.41$, 95% CI = 0.36 -0.45), and this association was robust to adjustment for baseline negative affect ($\beta = 0.11$, 95% CI = 0.05 – 0.17). These findings were supported by Hakulinen et al. (2015a) who performed similar analysis in an individual-participant meta-analysis of 10 studies including a total of 117,899 individuals with a follow-up time of 5 years. Cross-

sectional analysis showed an association between neuroticism and depressive symptoms ($\beta = 0.39$, 95% CI = 0.32 – 0.45). Longitudinal analysis indicated that higher neuroticism was associated with depressive symptoms at follow-up ($\beta = 0.12$, 95% CI = 0.10 – 0.13). To test for reverse causality, the association between baseline depressive symptoms and neuroticism at follow-up was examined, and the results showed that depressive symptoms at baseline were associated with higher neuroticism at follow-up ($\beta = 0.23$, 95% CI = 0.09 – 0.36). Both longitudinal models were adjusted for either depressive symptoms at baseline, or neuroticism at baseline. Together with the findings from Elovainio et al. (2015), this large meta-analysis suggests a reciprocal relationship between neuroticism and depressive symptoms, where both traits affect each other, leading to a negative spiral of increased risk for depressive symptoms and psychological vulnerability to depressive symptoms.

A longitudinal study, using data from the Finnish Hospital Discharge Register, examined the association between premorbid personality and later risk of schizophrenia or bipolar disorder (Lönnqvist et al., 2009). The results showed that each standard deviation increase in neuroticism was associated with a 26% increase in risk for schizophrenia (OR = 1.26, 95% CI = 1.19 – 1.34), after adjusting for birth year, test year, age at testing, and intelligence. No significant associations were found between neuroticism and bipolar disorder. The authors note that individuals who are hospitalized with a bipolar disorder diagnosis represent the most severe cases of the disorder. Many patients with bipolar disorder are unlikely to be hospitalized. Other studies have shown inconsistent results when examining the association between neuroticism and bipolar disorder (Akiskal et al., 2006; M. V. Christensen & Kessing, 2006; Jylhä et al., 2010). M. V. Christensen and Kessing (2006) showed that there was no association between neuroticism and bipolar disorder, while Akiskal et al. (2006) showed that individuals with bipolar disorder have significantly higher neuroticism scores compared to controls. This is supported by the findings from Jylhä et al. (2010), who showed that both individuals diagnosed with bipolar disorder or major depressive disorder had significantly

higher neuroticism scores than the general population. No differences in neuroticism scores were found between individuals diagnosed with bipolar disorder or major depressive disorder. This suggests that neuroticism might indicate vulnerability for mood disorders in general, including both bipolar disorder and major depressive disorder.

Kotov et al. (2010) argued that individual differences in neuroticism might be the key to understanding comorbidity amongst mental disorders, as neuroticism has been shown to be associated with different mental disorders (Malouff et al., 2005). Khan, Jacobson, Gardner, Prescott, and Kendler (2005) showed that neuroticism accounted for an average of 26% of the pair-wise comorbidity between mental disorders (range between 12 – 88%), which included major depressive disorder, anxiety disorder, panic disorder, substance use disorder, and personality disorders. Similar results were found when examining comorbidity for both mental and physical disorders, where neuroticism accounted for a substantial proportion of the comorbidity within mental disorders and within physical disorders (Neeleman, Ormel, Bijl, Neeleman, & Ormel, 2001).

2.5.4. Fatigue

Watson and Pennebaker (1989) have suggested that neuroticism is a measure of psychological distress, and several studies have shown that individuals who report more psychological distress, are more likely to experience medically unexplained symptoms and disorders (I. J. Deary, 1999; I. J. Deary, Scott, & Wilson, 1997), such as fatigue (De Gucht, Fischler, & Heiser, 2004; Henningsen, Zimmermann, & Sattel, 2003). For example, De Gucht et al. (2004) showed that negative affect is the strongest determinant of symptom evolution and persistence in patients who reported medically unexplained symptoms, including fatigue. A meta-analytic review showed that chronic fatigue syndrome was characterised by two measures of psychological distress, i.e. depressive symptoms and anxiety (Henningsen et al., 2003).

Buckley et al. (1999) examined personality in a small study including 30 patients with chronic fatigue, 20 patients with major depressive disorder, and 15 healthy controls, and found increased levels of neuroticism in both patients with major depressive disorders and chronic fatigue syndrome, compared to the healthy controls. A study examining the association between personality and fatigue symptoms found that neuroticism and fatigue are strongly related, individuals who scored higher on neuroticism reported more fatigue symptoms (De Vries & Van Heck, 2002). These findings are supported by other studies examining the association between neuroticism and fatigue, reporting higher levels of neuroticism in individuals with fatigue symptoms (V. Deary & Chalder, 2010; Taillefer, Kirmayer, Robbins, & Lasry, 2003; Tobback et al., 2016). All these studies indicate that psychological distress, as measured by neuroticism, is associated with fatigue. As shown by Henningsen et al. (2003), depression is also a common factor associated with fatigue, and some of the symptoms in chronic fatigue syndrome are similar to major depressive disorder symptoms (van Geelen, Sinnema, Hermans, & Kuis, 2007). Valero, Sáez-Francàs, Calvo, Alegre, and Casas (2013) examined the associations between neuroticism, depressive symptoms, and fatigue using structural equation modelling. They found that the effect of neuroticism on fatigue was mediated by depressive symptoms. Most studies examining the association between neuroticism and fatigue have a cross-sectional design, which means that their ability to unravel the direction of association between neuroticism and fatigue is limited. Two longitudinal studies using the Swedish Twin Registry Study, which comprises all twin births in Sweden since 1886 (Lichtenstein et al., 2002), showed that higher premorbid neuroticism levels were associated with both reporting more fatigue symptoms (Charles, Gatz, Kato, & Pedersen, 2008) and higher risk of chronic fatigue syndrome (Kato, Sullivan, Evengård, & Pedersen, 2006) after a follow-up time of 25 years. Each standard deviation increase in neuroticism was associated with 55 – 72% increase in risk of chronic fatigue syndrome in an unselected population. This effect was slightly attenuated when analysing monozygotic and dizygotic twins, but remained significant, the effect became non-significant when analysing

monozygotic twins only. The authors suggest that this implicates that the associations between neuroticism and fatigue could be due to a shared genetic background.

2.5.5. Neuroticism and health mechanisms

Given the robust association between neuroticism and health outcomes, it is important to understand and discover potential mechanisms underlying this association. While multiple different mechanisms have been proposed (Figure 2-3), this Section will focus on health behaviours, physiological responses, and a shared biological background, as indicated by the second and third causal models in Figure 2-3.

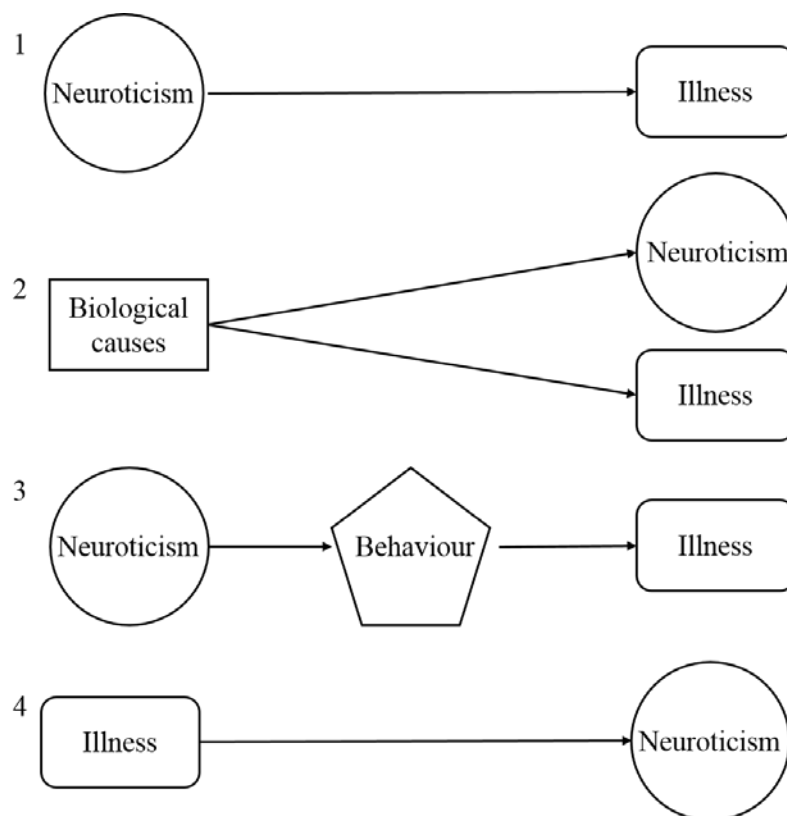


Figure 2-3. Four causal models for associations between neuroticism and health. Adapted with permission from G. Matthews et al. (2009). Copyright by Cambridge University Press (2009).

As personality traits are directly linked to behaviour (G. Matthews et al., 2009), it is possible that certain health-promoting or health-harming behaviours associated with prior personality dispositions thereafter directly affect health, thereby mediating the association between neuroticism and health. Previous research has indicated that individuals with higher neuroticism are more likely to smoke (Hakulinen et al., 2015b) or suffer from substance use disorders (Larkins & Sher, 2006), which could lead to increased risk of developing cardiovascular risk factors, cardio-metabolic diseases, or cancer (Lahey, 2009). High neuroticism has also been linked to a lack of physical activity (Wilson & Dishman, 2015). As discussed in Section 2.5.3, high neuroticism predisposes individuals to increased risk of developing mental health disorders, which could be improved by physical activity. Individuals with higher neuroticism are more likely to engage in unhealthy eating habits (T. W. Smith & MacKenzie, 2006), which increases risk for higher body weight (Torres & Nowson, 2007), in itself a strong risk factor for cardio-metabolic diseases. This indicated that health behaviours could potentially mediate the association between neuroticism and health. Formal tests have shown that mediation by health behaviours only explains a small part of the association between neuroticism and health (Chapman, Fiscella, Kawachi, & Duberstein, 2010; Mroczek, Spiro, & Turiano, 2009; Weiss, Gale, Batty, & Deary, 2009), suggesting that other processes might underlie the association between neuroticism and health

The experience of psychological stress has been linked to the activation of the HPA axis (S. Cohen, Janicki-Deverts, & Miller, 2007). Previous research has provided some evidence that the physiological responses to stress are moderated by neuroticism (Evans et al., 2016; Norris, Larsen, & Cacioppo, 2007). Activation of the HPA axis leads to the release of classical stress hormones such as adrenaline, noradrenaline, and cortisol. Chronic stress exposure could have damaging effects on the HPA axis, as cortisol regulates various physiological processes, including anti-inflammatory responses, metabolism of carbohydrates, fats, and proteins, and

gluconeogenesis. Stress could therefore lead to an increase in body fat and insulin resistance (Kyrou, Chrousos, & Tsigos, 2006).

Health behaviours and physiological responses to stress might partly explain the associations between neuroticism and health outcomes. The spectrum model, used in depression research, hypothesized that high neuroticism and depression cover similar constructs with different names, also called a ‘jangle’ fallacy (Kelley, 1927). The robust association of neuroticism, not just with depression, but also with other indicators of negative emotions such as fatigue and anxiety, suggests that all these traits represent a general state of psychological distress, which could partly be influenced by an underlying biological background. The next Section will discuss the potential shared genetic aetiology of neuroticism and health.

2.6. Negative emotions and health: genetics

Several mechanisms have been proposed to explain the relationship between neuroticism and health outcomes, as discussed in Section 2.5.5 of this Chapter. This thesis will focus on the shared genetic aetiology between negative emotions and health, to better understand the pathways between health and disease. But before we can discuss the shared genetic aetiology it is important to understand the genetic aetiology of neuroticism itself. This Section of Chapter 2 will therefore start by discussing the genetic aetiology of neuroticism using twin studies, SNP based studies, and association analyses. This will be followed by the shared genetic aetiology between neuroticism and health outcomes. The theoretical background of the different techniques used in these studies was outlined in Section 1.3.

2.6.1. Genetic aetiology of neuroticism

The field of behavioural genetics has produced many studies on the heritability of neuroticism (Birley et al., 2006; Bouchard & Loehlin, 2001; Hahn, Johnson, & Spinath, 2013; Keller,

Coventry, Heath, & Martin, 2005; Vukasović & Bratko, 2015; Wray, Birley, Sullivan, Visscher, & Martin, 2007) and has shown the heritability to be around 40%. A large meta-analysis of 113,452 individuals from 62 independent studies showed that 39% of the variance in neuroticism was due to genetic effects, using both the Five Factor Model and Eysenck's personality framework (Vukasović & Bratko, 2015). No evidence was found for differential heritability based on the personality model that was used, nor did sex have a moderating effect on the heritability estimates. This supports earlier findings, using 4731 twins from the Netherlands Twin Register, by Wray et al. (2007) who did not find any sex differences in the genetic aetiology of neuroticism. The same study also showed strong genetic correlations (> 0.9) between four measures of neuroticism taken over a period of 22 years in more than 20,000 individuals from 4999 families, indicating that the effects of age on the genetic contributions to neuroticism are likely to be small. It is important to note that the meta-analysis by Vukasović and Bratko (2015) showed that the heritability estimates from family and adoption studies ($h^2 \sim 22\%$) were lower than the estimates from adoption studies ($h^2 \sim 47\%$). This could indicate the importance of non-additive genetic effects, as heritability estimates from twin studies include both additive and non-additive genetic effects, whereas family and adoption studies only include additive genetic effects. The contribution of non-additive genetic effects for neuroticism have been estimated to be up to half of the genetic variance (Hahn et al., 2013; Keller et al., 2005; Plomin, Corley, Caspi, Fulker, & DeFries, 1998).

The heritability of neuroticism based on common genetic variants, using both GCTA-GREML and linkage disequilibrium score regression (LDSR), has been estimated to be around 15% (Genetics of Personality Consortium, 2015; Lo et al., 2017; Power & Pluess, 2015; Realo et al., 2016; D. J. Smith et al., 2016). The largest study to date (D. J. Smith et al., 2016) included 91,370 individuals from UK Biobank and reported the heritability of neuroticism to be 13.6% ($SE = 1.5\%$) using LDSR, and 15.6% ($SE = 0.7\%$) using GCTA-GREML. This study also showed similar heritability estimates for both males ($h^2 = 13.5\%$, $SE = 2.4\%$) and females (h^2

= 14.9%, SE = 1.7%), as well as a genetic correlation of 0.91 (SE = 0.07) between the two sexes. This suggest that the sex difference in neuroticism scores, as discussed in Section 2.4, is not due to common genetic variants, but more likely to environmental factors, gene-gene interactions, gene-environment interactions, or rare genetic variants for example.

2.6.2. Genome-wide association studies

Early molecular genetic research into genetics variants' effect on neuroticism, using candidate gene studies, focussed on genes potentially involved in the HPA-axis, such as dopamine, serotonin, and oxytocin; however, these studies did not find consistent evidence for an association with neuroticism, possibly due to underpowered studies, differences in personality questionnaires, or gene-environment interactions (Montag & Reuter, 2014). GWAS have been a little more successful in identifying genetic variants associated with neuroticism. A GWAS meta-analysis of 63,611 individuals from the Genetics of Personality Consortium (GPC) identified one SNP in the *MAGII* gene to be associated with neuroticism at a genome-wide significance level, but did not replicate in independent cohorts (Genetics of Personality Consortium, 2015). *MAGII* is primarily expressed in neuronal tissue in the hippocampus (Ito et al., 2012) and has previously been associated with several psychiatric disorders, such as schizophrenia, bipolar disorder, and major depressive disorder (Etain et al., 2006; Ferentinos et al., 2014; Karlsson et al., 2012). One GWAS has analysed the X-chromosome in 2168 individuals, but did not find any genome-wide significant findings (Calboli et al., 2010).

D. J. Smith et al. (2016), using the UK Biobank sample, reported nine genome-wide significant loci in genes which for example have been implicated in the HPA axis (*CRHRI*) and the glutamate system (*GRIK3*). Both pathways are involved in the body's stress response and the two genes have been linked to major depressive disorder, anxiety, and panic disorder (Gray, Hyde, Deep-Soboslay, Kleinman, & Sodhi, 2015; P. H. Lee et al., 2012; Stetler & Miller,

2011; Weber et al., 2016). The largest GWAS to date for neuroticism combines the participants from both the GPC and UK Biobank, leading to a total sample size of 170,911 individuals (Okbay et al., 2016a). This GWAS identified 11 genome-wide significant loci of which four were also nominally significant in a GWAS of major depressive disorder and subjective well-being. The effect sizes of the genome-wide significant SNPs in these GWAS were all very small, therefore supporting a polygenic architecture of neuroticism. The findings discussed in this paragraph indicate a shared genetic aetiology between neuroticism and psychiatric disorders.

2.6.3. Shared genetic aetiology neuroticism and health

2.6.3.1. Physical health

Evidence of a shared genetic aetiology between neuroticism and physical health is relatively sparse. A family study including 6148 individuals from Sardinia did not find any evidence for a shared genetic aetiology between neuroticism and a range of cardiovascular traits (Pilia et al., 2006). Similarly, a twin study of 3752 twins examining the genetic association between neuroticism and mortality did not find an association between the two. Where twin and family studies have been unable to capture a possible shared genetic aetiology between neuroticism and physical health, molecular genetic methods have had more success. Okbay et al. (2016a) used LDSR to examine the genetic association between neuroticism and physical health and reported significant genetic correlations between neuroticism and coronary artery disease ($r_g = 0.13$, $SE = 0.04$), smoking ($r_g = 0.13$, $SE = 0.04$), and triglycerides ($r_g = 0.07$, $SE = 0.03$), as shown in Figure 2-4C. The genetic correlation between neuroticism and these traits is relatively small and the traits themselves have a low heritability ($h^2 < 0.12$) (J. Zheng et al., 2016). This means that the co-heritability is likely to be low as well (see Section 1.3.1.6), indicating that the proportion of the variation in neuroticism accounted for by the additive genetic components to the physical health traits is likely also to be small. This is supported by

the findings of Harris et al. (2016a), who showed that polygenic profile scores for neuroticism explained 0.03% of the variance in self-rated health, which itself shows great genetic overlap with physical health traits, as well as a genetic correlation of -0.38 (SE = 0.07) between neuroticism and self-rated health. A small study of 837 individuals from the Lothian Birth Cohort 1936 did not find an association between polygenic risk for type 2 diabetes and neuroticism (Čukić et al., 2015).

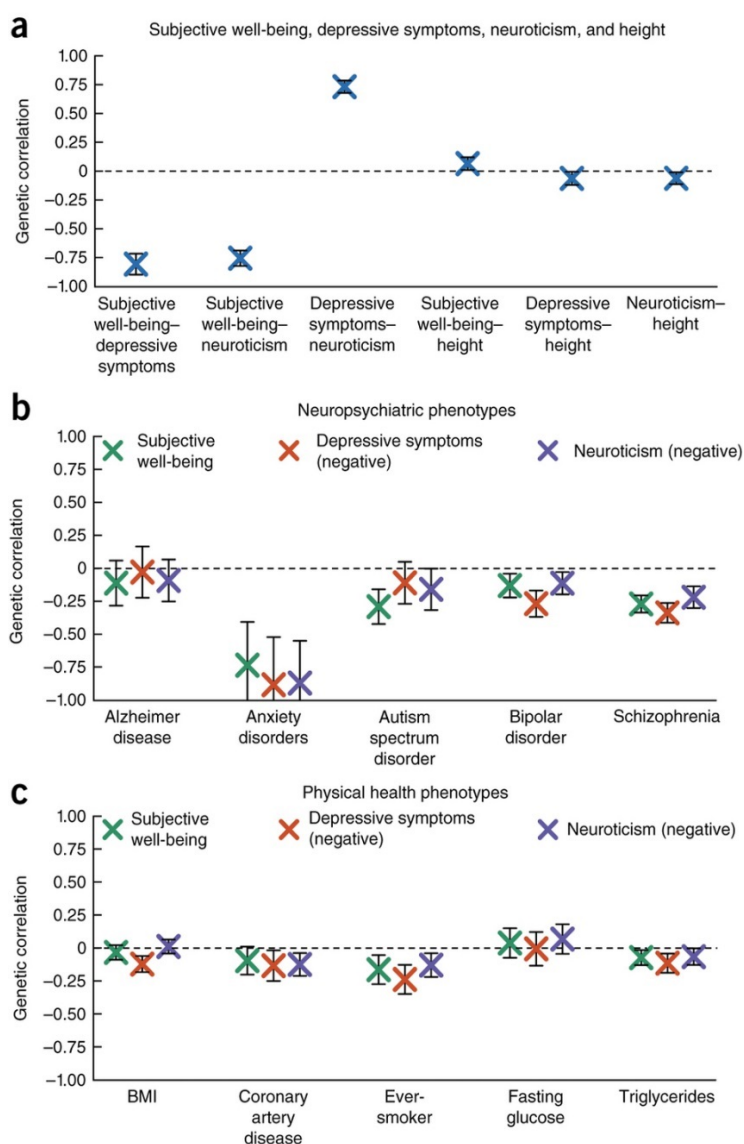


Figure 2-4. Correlations were estimated using bivariate LD Score (LDSC) regression. (a) Genetic correlations between subjective well-being, depressive symptoms, and neuroticism ('our three phenotypes'), as well as between our three phenotypes and height. (b) Genetic correlations between

our three phenotypes and selected neuropsychiatric phenotypes. (c) Genetic correlations between our three phenotypes and selected physical health phenotypes. In b and c, we report the negative of the estimated correlation with depressive symptoms and neuroticism (but not subjective well-being). Error bars represent 95% confidence intervals. Reprinted with permission from Okbay et al. (2016a). Copyright 2016 by Springer Nature.

2.6.3.2. Mental health

As discussed in Section 2.5.3 neuroticism is strongly associated with low mood, anxiety and psychological distress, and all these traits possibly cover the same general trait of negative emotions. It is therefore not surprising that a wide range of studies have explored the shared genetic aetiology between neuroticism and mental health. Twin studies reported genetic correlations between neuroticism and major depressive disorder of 0.43 in 542 twins (Kendler & Myers, 2010), 0.46 in 7831 twin pairs (Kendler, Gatz, Gardner, & Pedersen, 2006), and 0.60 in 9270 twins (Hettema, Neale, Myers, Prescott, & Kendler, 2006). Molecular genetic studies have also reported a shared genetic aetiology between neuroticism and major depressive disorder; polygenic profiles for neuroticism explained 0.1% of the variance in major depressive disorder (Middeldorp et al., 2011). The polygenic profiles in this study were based on GWAS of neuroticism including 13,835 individuals and predicted in to 8921 individuals, which might limit the predictive power of this analysis. Using a much larger GWAS, based on 63,661 individuals, polygenic profiles for neuroticism explained 1.05% of the variance in major depressive disorder (Genetics of Personality Consortium, 2015). While the amount of variance explained is small, it should be considered the minimum amount of variance explained, as per Section 1.3.1.7. These results support the findings by Okbay et al. (2016a), who reported a genetic correlation of 0.75 ($SE = 0.03$) between neuroticism and depressive symptoms (Figure 2-4A). Major depressive disorder and anxiety are highly comorbid and it is therefore likely that anxiety disorders also show a shared genetic aetiology with neuroticism. Hettema et al. (2006) showed a genetic correlation of 0.77 between neuroticism and anxiety disorders, and of 0.69 between neuroticism and panic disorder in 9270 twins. In a behavioural

genetics study of 23,280 twins, neuroticism accounted for approximately 25% of the genetic correlation between major depressive disorder and anxiety, which indicated that all these traits are genetically related to each other (Kendler, Gardner, Gatz, & Pedersen, 2007). No differences have been found in the genetic correlations between neuroticism and anxiety disorder between males and females (Hettema, Prescott, & Kendler, 2004), which is in line with the finding that the heritability for neuroticism for males and females is similar (D. J. Smith et al., 2016).

With major depressive disorder and anxiety on the negative end of the scale, it could be said that subjective well-being can be found on the positive end of the scale. In line with that, Okbay et al. (2016a) found a significant negative genetic correlation between neuroticism and subjective well-being ($r_g = -0.75$, $SE = 0.03$), which is higher than the genetic correlation reported by Weiss et al. (2016) between neuroticism and positive affect ($r_g = -0.55$, $SE = 0.09$), and between neuroticism and life satisfaction ($r_g = -0.49$, $SE = 0.07$). This discrepancy in results for traits that are strongly associated is potentially due to the different methods being used (GCTA-GREML in the study of Weiss et al. (2016) compared to LDSR by Okbay et al. (2016a)), as well as the difference in sample size. The genetic correlation reported by Okbay et al. (2016a) was based on a GWAS for neuroticism which included 170,911 individuals and a GWAS for subjective well-being which included 298,420 individuals, while the genetic correlation reported by Weiss et al. (2016) was based on a total sample of 30,367 individuals.

Limited evidence is available to indicate a genetic overlap between neuroticism and bipolar disorder or schizophrenia. Middeldorp et al. (2011) did not find a significant association between polygenic profiles for neuroticism and bipolar disorder in 6329 individuals, but a significant genetic correlation was found between neuroticism and bipolar disorder ($r_g = 0.11$, $SE = 0.04$) using LDSR. As can be seen in Figure 2-4B, the same study also reported a significant genetic correlation between neuroticism and schizophrenia ($r_g = 0.22$, $SE = 0.04$),

which supports results by Macare, Bates, Heath, Martin, and Ettinger (2012) who reported that 51 % of the phenotypic correlation between schizotypy, defined as attenuated schizophrenia-like traits, and neuroticism is explained by genetic factors.

2.7. Summary

This Chapter provided an introduction to the second part of this thesis; negative emotions, and its associations with health outcomes, both on a phenotypic and genetic level. The empirical work in the second part of this thesis will address the following key question:

- 1) Do the tendency to experience negative emotions and health have some shared genetic aetiology?

Empirical evidence for this key question will be provided in Chapters 6 and 7 relating to: the shared genetic aetiology between neuroticism and physical and mental health; and the shared genetic aetiology between self-reported tiredness and physical and mental health, with a focus on neuroticism. First, however, Chapter 3 will next provide background on the main cohort used in this study: UK Biobank.

3. UK Biobank

3.1. Introduction

This Chapter describes the methodology used by the UK Biobank, a health resource for researchers that aims to improve the prevention, diagnosis, and treatment of a range of illnesses (<http://www.ukbiobank.ac.uk>). It will include information about the study population, recruitment procedures and ethical approval. In addition, it will provide an in-depth discussion of the cognitive testing, measurements of negative emotions and the genetic data.

3.2. Baseline data

The UK Biobank is a population-based prospective study, set up as a resource for identifying determinants of disease in middle aged and older people. Between the years 2006 and 2010, about 500,000 individuals aged from middle age to older age were recruited throughout the United Kingdom, covering 22 assessment centres. This provided a spread in socioeconomic status and ethnicity, as well as an urban and rural mix. Data were collected on cognitive functions, physical and mental health, lifestyle, socio-demographic information, food intake, and family medical history. Data collection also involved collecting biological samples.

3.2.1. Study population

UK Biobank sent out invitations to around 9.2 million individuals aged between 40 and 69, who were registered with the National Health Service and were living up to 25 miles away from one of the 22 assessment centres. With a response rate of 5.47%, a total of 503,325 participants were recruited. At the first visit to the assessment centre (2006 – 2010) all participants completed multiple questionnaires covering the following topics: socio-demographics, family history and early life exposures, psychosocial factors, environmental factors, lifestyle, health status, hearing threshold, and cognitive function. Physical

measurements included blood pressure, heart rate, hand grip strength, anthropometry, spirometry, bone density, arterial stiffness, a fitness test, and an eye examination. Blood, urine and saliva were collected for DNA extraction and biomarker measurement (Allen et al., 2012). Between 2014 and 2015 around 120,000 participants completed additional tests, including questionnaires on cognitive ability and work environment, diet by 24-hour recall, and physical measurement activity. In June 2015 UK Biobank released an interim dataset of the genetic data including 152,729 individuals, and this sample will be used throughout this Thesis.

3.2.2. Ethical approval

UK Biobank received ethical approval from the National Health Service National Research Ethics Committee (REC), under the reference 11/NW/0382. All participants provided written consent prior to assessment, which will apply throughout the lifetime of UK Biobank unless the participant withdraws.

3.2.3. Demographics

In total, 121,151 individuals (of 152,729 individuals) remained after quality control of the data (see Section 3.5.2 for details). The mean (SD) age was 56.91 (7.93) years with a range between 40 and 73 years. The dataset consisted of 58,914 females and 53,237 males. The age-sex distribution can be found in Figure 3-1. Table 3-1 displays the distribution of qualifications in UK Biobank, in which 30.2% of all participants had a college or university degree. All participants were asked at what age they completed continuous full time education; however, this excluded individuals who indicated they had a college or university degree. The mean (SD) age for completing secondary education was 16.4 (2.9) years.

Table 3-1. Distribution of qualifications in UK Biobank based on data from the first release of genetic data.

Qualification	Number of individuals	% Females
College/University degree	33,852	50.57
A/AS levels	12,560	56.18
0 levels/GCSEs	24,802	58.21
CSEs	6064	52.03
NVQ/HND/HNC	7788	34.17
Other professional qualifications	5776	58.89
None of the above	20,272	52.67
Prefer not to answer	953	51.10

Socioeconomic status has been measured in UK Biobank using the Townsend deprivation index, a measure of material deprivation (Townsend, Phillimore, & Beattie, 1988). The Townsend deprivation index is calculated from Census data and is a standardised composite score based on non-home ownership, unemployment over the age of 16, non-car ownership, and the number of individuals in each home. A greater Townsend score indicates a greater degree of deprivation. The mean (SD) Townsend deprivation index in UK Biobank was -1.49 (2.98), ranging between -6.26 and 10.78. The distribution by sex is displayed in Figure 3-1. Figure 3-2 shows the comparison between UK Biobank and the general population based on the Census data. The age distribution shows that UK Biobank is oversampled for older individuals compared with the 2011 Census. The Townsend deprivation index distribution shows that UK Biobank is a little more posh than the general population based on the 2001 Census, with more individuals in the lower Townsend score group and less in the higher groups. It is important to note that for the Townsend deprivation index the most updated Census data was from 2001, which at the time of writing is more than 15 years old. It is therefore possible that the difference at the current time is smaller or larger than at the 2001 Census.

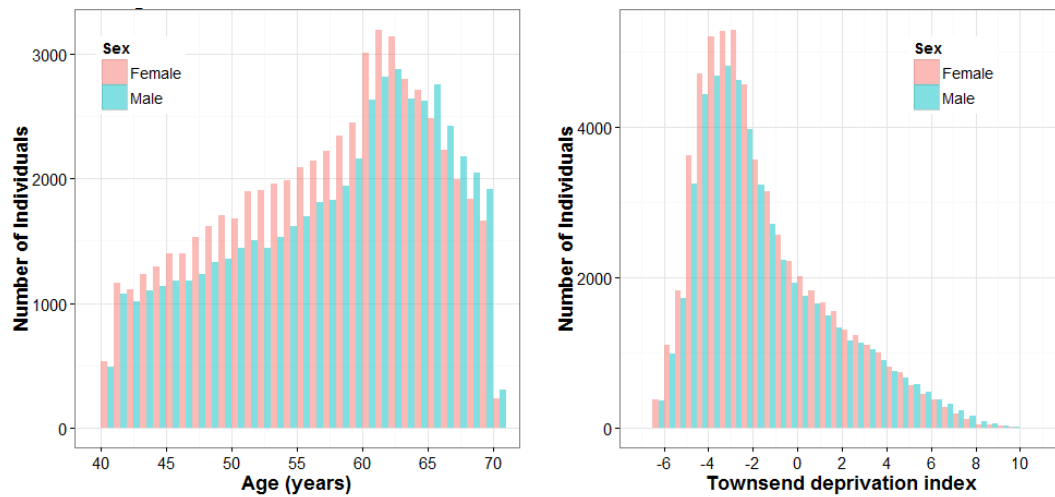


Figure 3-1. Left, age by sex distribution in UK Biobank; right, Townsend deprivation index by sex distribution in UK Biobank.

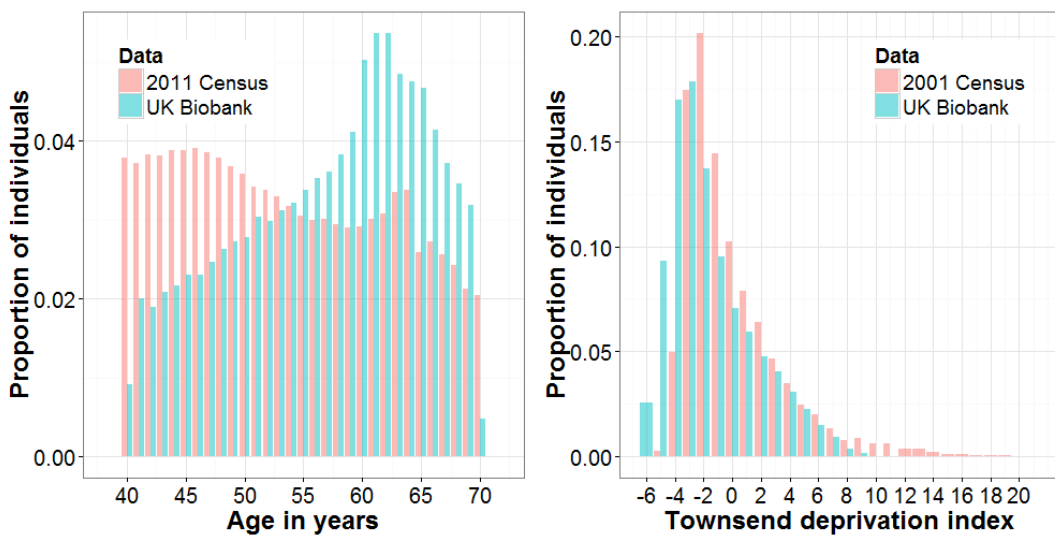


Figure 3-2. Left, comparison of age distribution in UK Biobank and in the United Kingdom based on the 2011 Census; right, comparison of the Townsend deprivation index in UK Biobank and in the United Kingdom based on the 2001 Census.

3.3. Cognitive testing

3.3.1. Reaction time

Reaction time was measured by a computerized ‘snap’ game during baseline testing (Figure 3-3). In this game, participants are shown two cards with simple symbols (e.g. an equal sign or square) at the same time, and are asked to press a button, with their dominant hand, as

quickly as possible when the two cards on the screen match. This game consisted of 12 trials (each with one pair of cards); the first four trials were regarded as ‘exercise’, resulting in eight experimental trials. From these eight experimental trials, four trials had matching cards and thus required the button to be pressed.

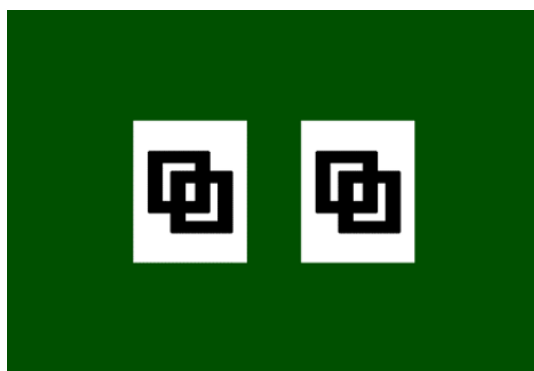


Figure 3-3. Reaction time test in UK Biobank. Participants were asked to press a button as quickly as possible when the symbols on the cards matched. Adapted with permission from UK Biobank (2013b). Copyright by UK Biobank 2013.

Each participant’s reaction time (in ms) was calculated as the mean time to press the button for the four experimental trials with matching cards. A general test of reaction time would normally include at least 20 trials (I. J. Deary, Der, & Ford, 2001; Der & Deary, 2006). Times over 2000 ms were disregarded before calculating the means, as the cards had disappeared from the screen by then. The mean (SD) reaction time was 555.1 (112.7) ms, with a range between 63 and 1905 ms. One participant was removed from all analysis because of an outlying reaction time (1905 ms, 12 standard deviations above the mean reaction time). Owing to a positively skewed distribution, all mean scores were log-transformed before further analysis. Figure 3-4 shows the distribution of reaction time before and after the logarithmic transformation, showing a more normal distribution after the logarithmic transformation.

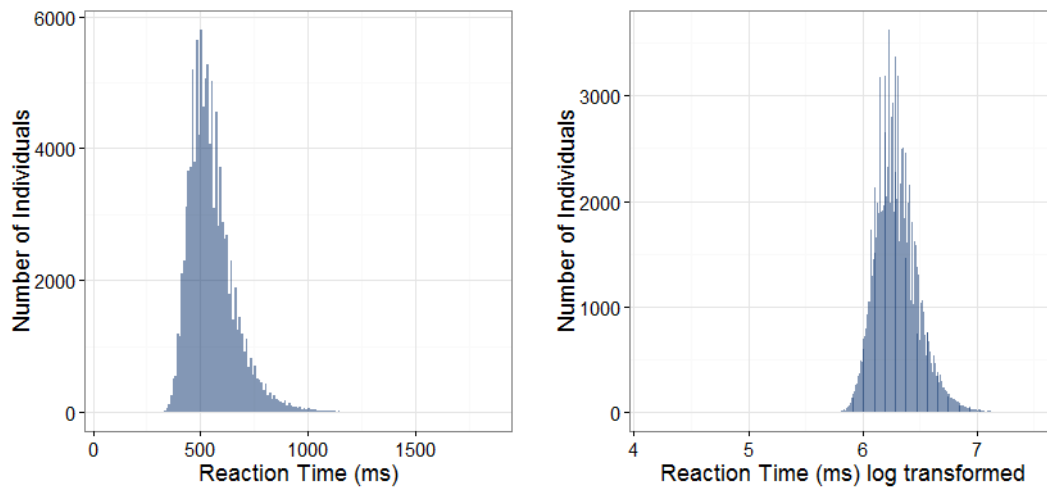


Figure 3-4. Distribution of reaction time; left, untransformed; right log transformed and outliers excluded.

The Cronbach alpha coefficient showed an internal consistency of 0.85 (Hagenaars et al., 2016b). Reaction time showed moderate stability over time, with an intraclass correlation of 0.57 (95% CI = 0.56 to 0.58) over a period ranging from two to seven years (Lyall et al., 2016). Reaction time scores are flipped for the ease of interpretation; a higher score indicates better reaction time. Figure 3-5 shows a linear decline in this reaction time measure between the ages of 40 and 70 years, with longer reaction times in older age, as well as a linear decline for the Townsend deprivation index with longer reaction times for individuals with higher Townsend scores (lower socio-economic status). Figure 3-6 shows that the average reaction time is worse for individuals with lower qualifications. Overall, males have better reaction times than females. A total of 111,483 individuals with genetic data the reaction time task.

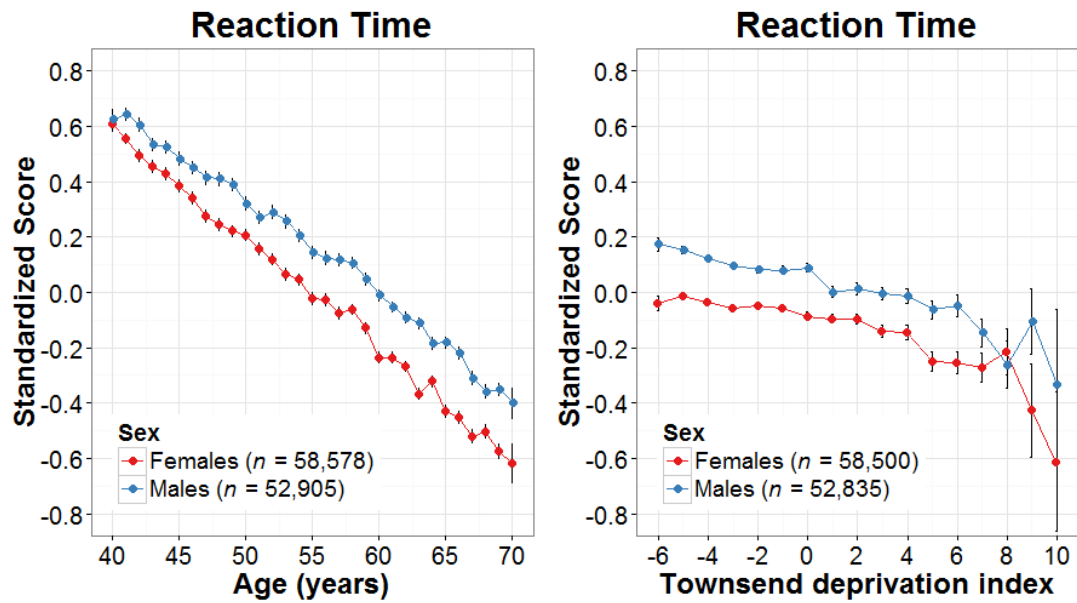


Figure 3-5. Age and Townsend deprivation index distribution for reaction time separated by sex. Error bars represent +/- one standard error of the mean. Higher scores indicate better performance on the reaction time test.

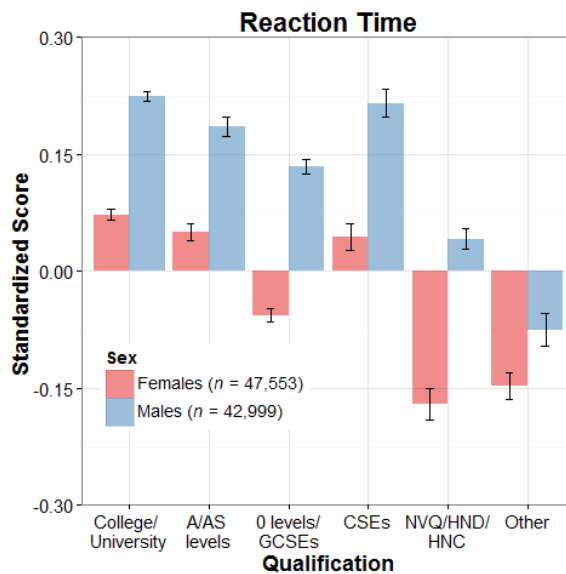


Figure 3-6. Qualifications distribution for reaction time separated by sex. Error bars represent +/- one standard error of the mean.

3.3.2. Memory

Memory was measured by a computerized 'pairs matching' game during baseline testing (Figure 3-7). The participant was shown a set of picture cards on a screen with matching pairs

and was asked to memorize the positions of as many pairs as possible. The picture cards were then turned over and no longer visible. The participant was asked to identify the matching pairs of cards, in the fewest number of attempts. Pairs were identified by touching the cards on the screen consecutively. The first round of the game included six cards (three pairs) that were shown for three seconds in a 2x3 grid. The second round of the game included 12 cards (six pairs) that were shown for five seconds in a 3x4 grid. To utilise the most information possible, this thesis will only use the 3x4 grid.

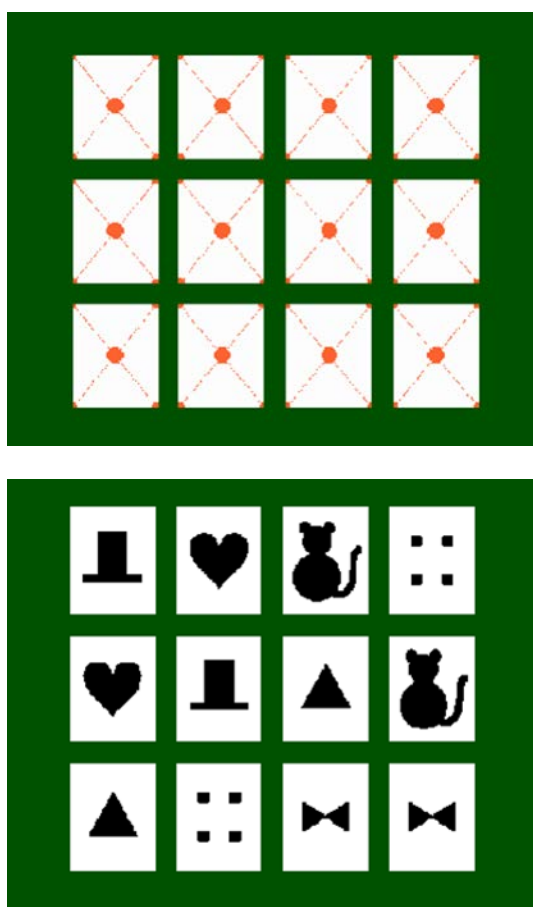


Figure 3-7. Pairs matching game in 3 x 4 grid in UK Biobank. Left, the cards turned down. Right, six pairs of matching cards are displayed to participants for five seconds. Adapted with permission from UK Biobank (2013a). Copyright by UK Biobank 2013.

Each participant's memory score was calculated as the number of errors made until all pairs of cards were correctly identified consecutively. The layout of the cards on the screen was at

random in each round. This game did not have a time restriction, i.e. the participants were able to identify pairs of cards until all matching pairs had been identified or they pressed the ‘abandon’ button. If the ‘abandon’ button was pressed, the participant was asked ‘Are you sure?’, when selecting ‘no’ they were returned to the current entry screen, when selecting ‘yes’, they continued with the next test. Figure 3-8 shows the distribution of the memory scores based on the smaller 2x3 grid, this grid has a clear ceiling effect, with 70% of the sample having no errors in the memory test. The 3x4 grid was more difficult and has less of a ceiling effect (Figure 3-9), this grid was therefore used in any further analysis. Twenty-nine individuals who made more than 30 errors had their number of errors set to 30 (winsorising). The distribution before and after winsorising are shown in Figure 3-9.

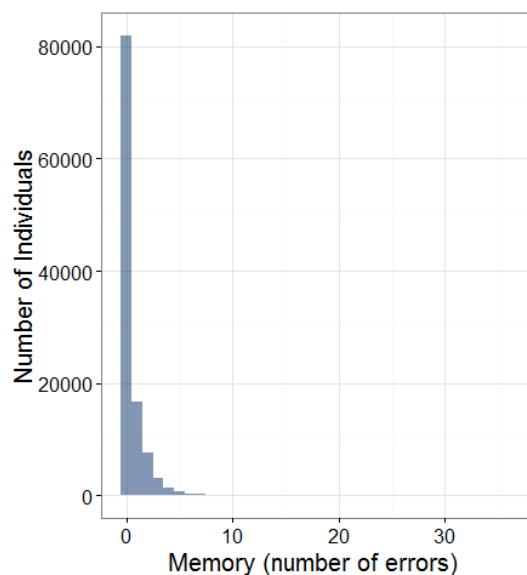


Figure 3-8. Distributions of memory scores based on the 2 x 3 grid.

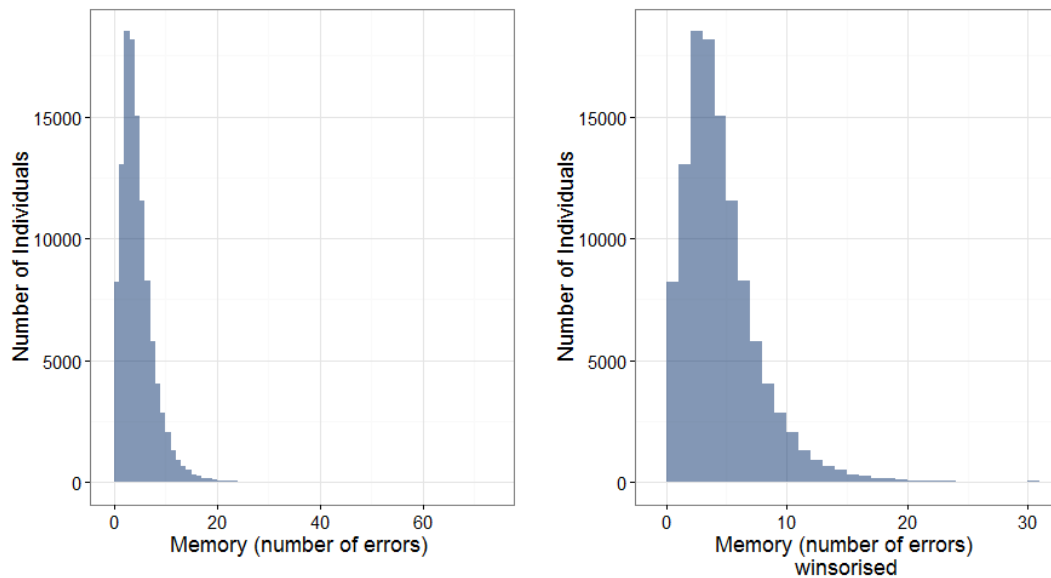


Figure 3-9. Distributions of memory scores based on the 3 x 4 grid; left, untransformed; right, winsorised.

This memory test showed low stability over a period of two to seven years, with an intraclass correlation of 0.16 (95% CI = 0.15 to 0.17) (Lyall et al., 2016). Memory scores are flipped for the ease of interpretation; a higher memory score indicates better performance on the test. Figure 3-10 shows a linear decline between the ages of 40 and 70 years, with more errors in older age, and very little differences across the Townsend deprivation index distribution. Figure 3-11 shows that individuals with lower qualifications make more errors compared to individuals with higher qualifications. Males and females have very similar performance on the test for memory across the differences distributions. A total of 112,067 individuals with genetic data completed the memory task.

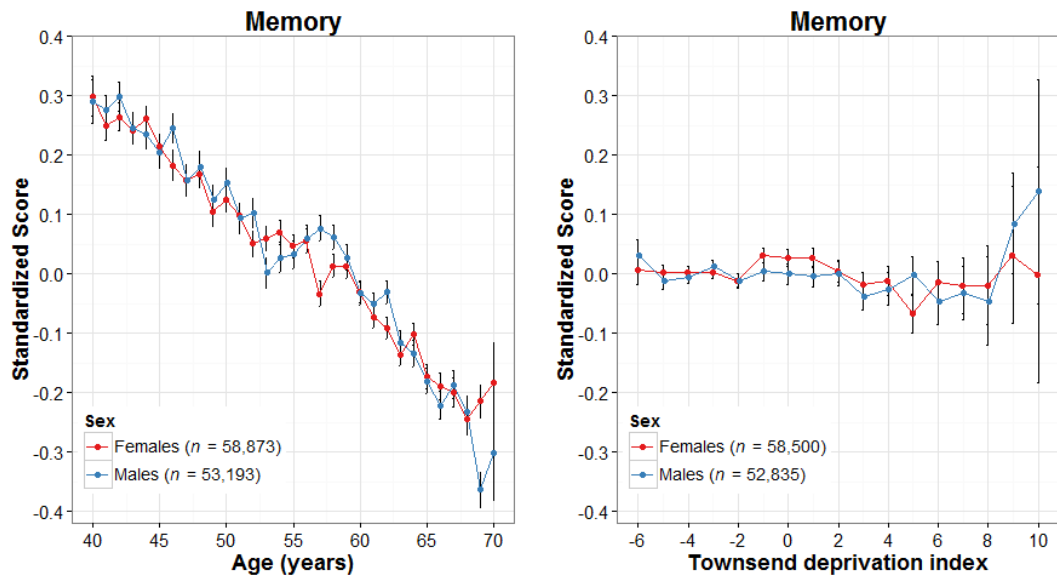


Figure 3-10. Age (left) and Townsend deprivation index (right) distribution for memory separated by sex. Error bars represent +/- one standard error of the mean. Higher scores indicate better memory performance.

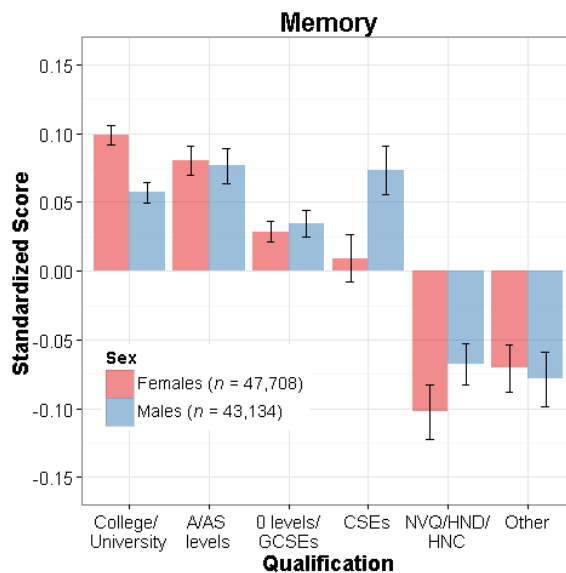


Figure 3-11. Qualifications distribution for memory separated by sex. Error bars represent +/- one standard error of the mean.

3.3.3. Verbal-numerical reasoning

To test each participant's ability to solve problems requiring reasoning ability and logic, a so-called 'fluid-intelligence' test was performed. This test was introduced at a later stage during baseline testing and only a subset of individuals therefore completed the verbal-numerical

reasoning questionnaire. This test comprised of thirteen multiple choice questions, which had to be answered within a two-minute time limit. The test included six verbal items and seven numerical items. All questions and the possible answers are shown in Table 3-2.

Table 3-2. Verbal-numerical reasoning questions and possible answers in UK Biobank.

Question	Possible answers
1. Add the following numbers together: 1 2 3 4 5 – is the answer?	13/14/15/16/17/Do not know/Prefer not to answer
2. Which number is the largest?	642/308/987/714/253/Do not know/Prefer not to answer
3. Bud is to flower as child is to?	Grow/Develop/Improve/Adult/Old/Do not know/Prefer not to answer
4. 11 12 13 14 15 16 17 18 Divide the sixth number to the right of twelve by three. Is the answer?	5/6/7/8/Do not know/Prefer not to answer
5. If Truda's mother's brother is Tim's sister's father, what relation is Truda to Tim?	Aunt/Sister/Niece/Cousin/No relation/Do not know/Prefer not to answer
6. If sixty is more than half of seventy-five, multiply twenty-three by three. If not subtract 15 from eighty-five. Is the answer?	68/69/70/71/72/Do not know/Prefer not to answer
7. Stop means the same as?	Pause/Close/Cease/Break/Rest/Do not know/Prefer not to answer
8. If David is twenty-one and Owen is nineteen and Daniel is nine years younger than David, what is half their combined age?	25 /26 /27 /28 /29 /Do not know /Prefer not to answer
9. Age is to years as height is to?	Long /Deep /Top /Metres /Tall /Do not know /Prefer not to answer
10. 150...137...125...114...104... What comes next?	96 /95 /94 /93 /92 /Do not know /Prefer not to answer
11. Relaxed means the opposite of?	Calm /Anxious /Cool /Worried /Tense /Do not know /Prefer not to answer
12. 100...99...95...86...70... What comes next?	50 /49 /48 /47 /46 /45 /Do not know /Prefer not to answer

13. If some flinks are plinks and some plinks are stinks then some flinks are definitely stinks? False True /Neither true nor false /Not sure /Do not know /Prefer not to answer
-

Each participant's score on the test was calculated as the overall score of the thirteen items in the test. The Cronbach alpha coefficient showed an internal consistency of 0.62. The intraclass correlation coefficient was 0.65 (95% CI = 0.63 – 0.67), indicating good stability of the test over a period of two to seven years (Lyall et al., 2016). Figure 3-12 shows the distribution of the scores. UK Biobank named this test the 'fluid-intelligence' test, comparable to the concept of fluid cognitive ability as proposed by Horn and Cattell (1966). One would, therefore, expect to see a steady age-related decline in the scores (Salthouse, 2010; Tucker-Drob, 2009). As can be seen in Figure 3-13, this test shows stable mean scores between the ages of 40 and 60 years, followed by a linear decline in mean scores between the age of 60 and 70 years. This pattern is somewhat similar to that of vocabulary tests, which are used to assess crystallized cognitive ability (Salthouse, 2004). Therefore, this test will be referred to by its contents, i.e. the verbal-numerical reasoning test.

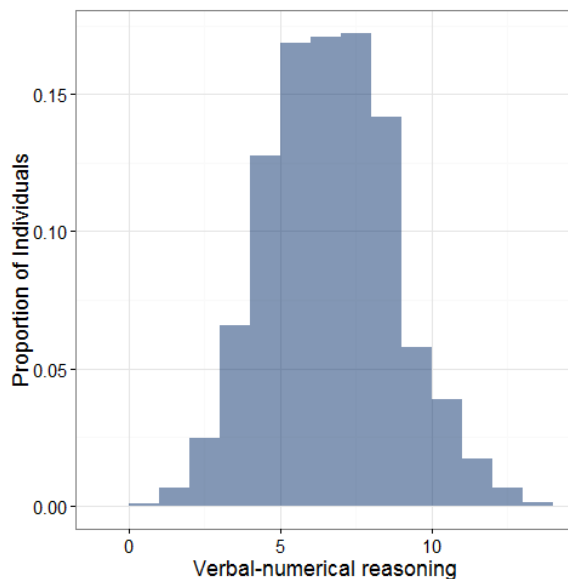


Figure 3-12. Distribution of the verbal-numerical reasoning scores.

Figure 3-13 shows a positive linear decline in mean scores for the Townsend deprivation index, indicating that individuals with a lower socio-economic status score lower on the verbal-numerical reasoning test. A similar pattern of decline can be seen in Figure 3-14, showing that individuals with higher educational attainment had better verbal-numerical reasoning performance. Males generally scored higher on the test of verbal-numerical reasoning than females. A total of 36,035 individuals with genetic data completed the verbal-numerical reasoning questionnaire.

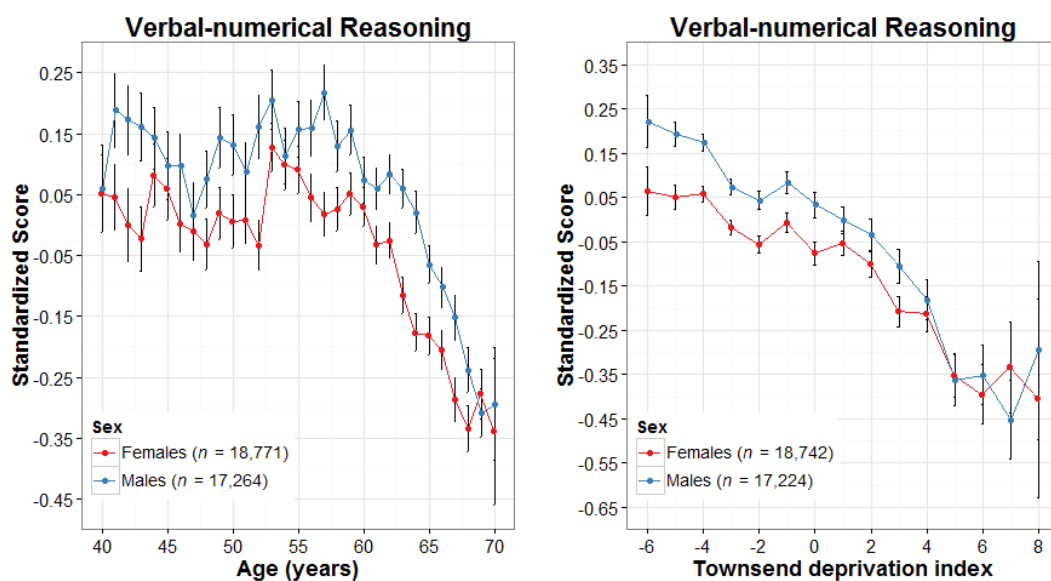


Figure 3-13. Age (left) and Townsend deprivation index (right) distribution for verbal-numerical reasoning separated by sex. Error bars represent +/- one standard error of the mean. Individuals with a Townsend deprivation index > 8 are not displayed in the graph due to the low N.

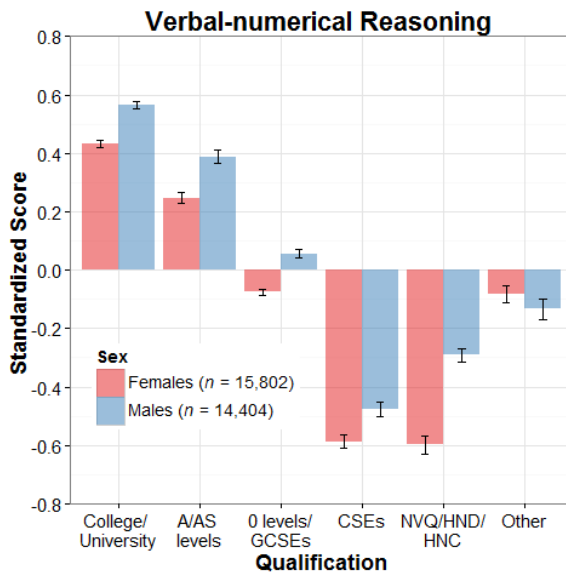


Figure 3-14. Qualifications distribution for verbal-numerical reasoning separated by sex. Error bars represent +/- one standard error of the mean.

3.3.4. Educational attainment

All participants completed a sociodemographic questionnaire during baseline testing, which included questions about educational attainment (UK Biobank, 2012). This thesis will use the question, ‘Which of the following qualifications do you have? (You can select more than one)’ (answers included: ‘College or University Degree/A levels or AS levels or equivalent/O levels or GCSE or equivalent/CSEs or equivalent/NVQ or HND or HNC or equivalent/Other professional qualifications e.g. nursing, teaching/None of the above/Prefer not to Answer’). The age and Townsend deprivations index distributions for all qualifications are shown in Figure 3-15. In order to indicate whether or not a participant had a college or university degree, a binary educational attainment variable was created. Educational attainment has shown to be a good proxy phenotype for cognitive ability as has been discussed in Section 1.3.2.5 (Rietveld et al., 2014), and college degree attainment will be used as such in this Section 4.2. A total of 111,114 individuals with genetic data answered the educational attainment question (Table 3-1).

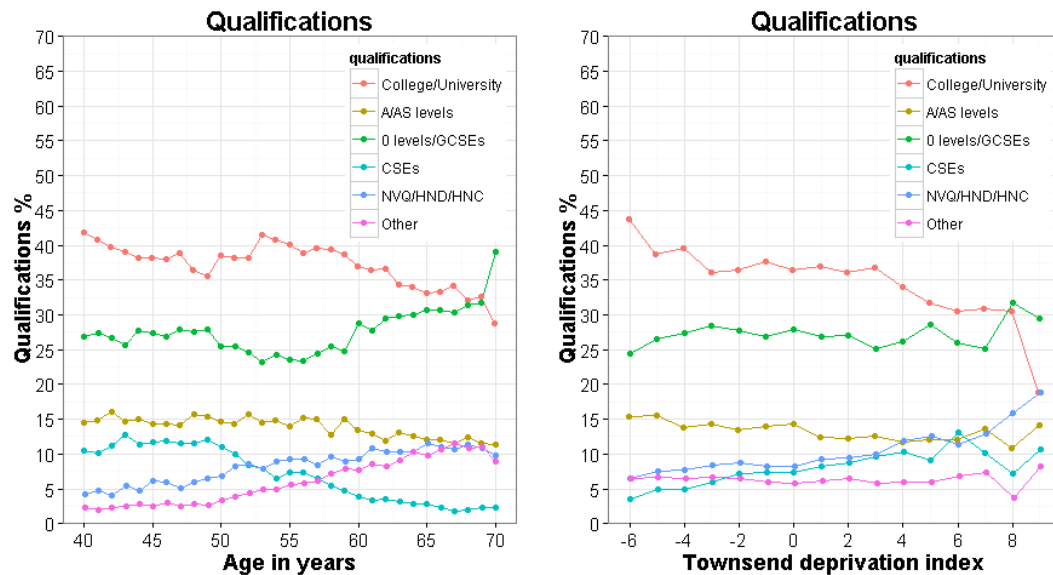


Figure 3-15. Age (left) and Townsend deprivation index (right) distribution for each type of qualifications. Individuals with a Townsend deprivation index > 9 are not displayed in the graph due to the low N.

3.3.5. Trail making test

Processing speed and executive functioning were assessed during the additional web-based follow up between 2014 and 2015, by the trail making test, part A (TMT A) and B (TMT B), among other tests. As this assessment was completed remotely, it is possible that participants used different technologies (for example using a tablet, touchpad or mouse) to complete the test. UK Biobank did not provide information on this. For TMT A, participants have to consecutively connect numbers (1 – 25) randomly distributed on the screen as quickly as possible by clicking on the next number (Figure 3-16). TMT B is similar, but in this case, letters (A – L) and numbers (1 – 13) have to be connected in ascending order, e.g. 1 A 2 B 3 C etc. (Figure 3-16).

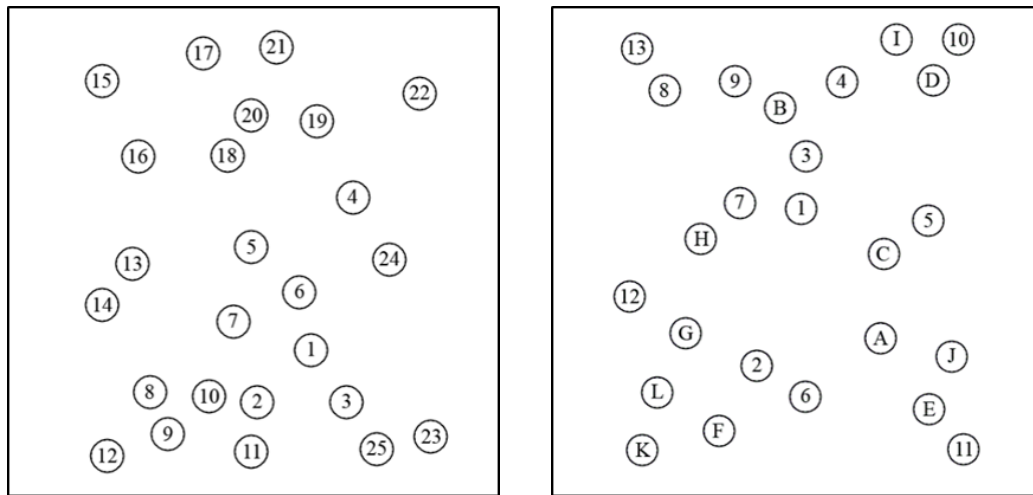


Figure 3-16. Trail Making Test Part A (left) and Trail Making Test Part B (right). Adapted with permission from UK Biobank (2015d). Copyright by UK Biobank 2015.

The intervals between touching two points was timed in seconds using a Javascript timer. The time (in seconds) to complete the trail making test (part A or B) was derived by summing the interval values between two points. Individuals who scored above 250 seconds for TMT B were excluded ($N = 9$). Owing to a positively skewed distribution, both TMT A and TMT B scores were log-transformed before further analysis (Figure 3-17). The differences between the scores for TMT A and TMT B was calculated by subtracting the untransformed scores for TMT A from TMT B ($\text{TMT B} - \text{A}$). Individuals who scored <-50 or >150 seconds were removed from $\text{TMT B} - \text{A}$ ($N = 52$).

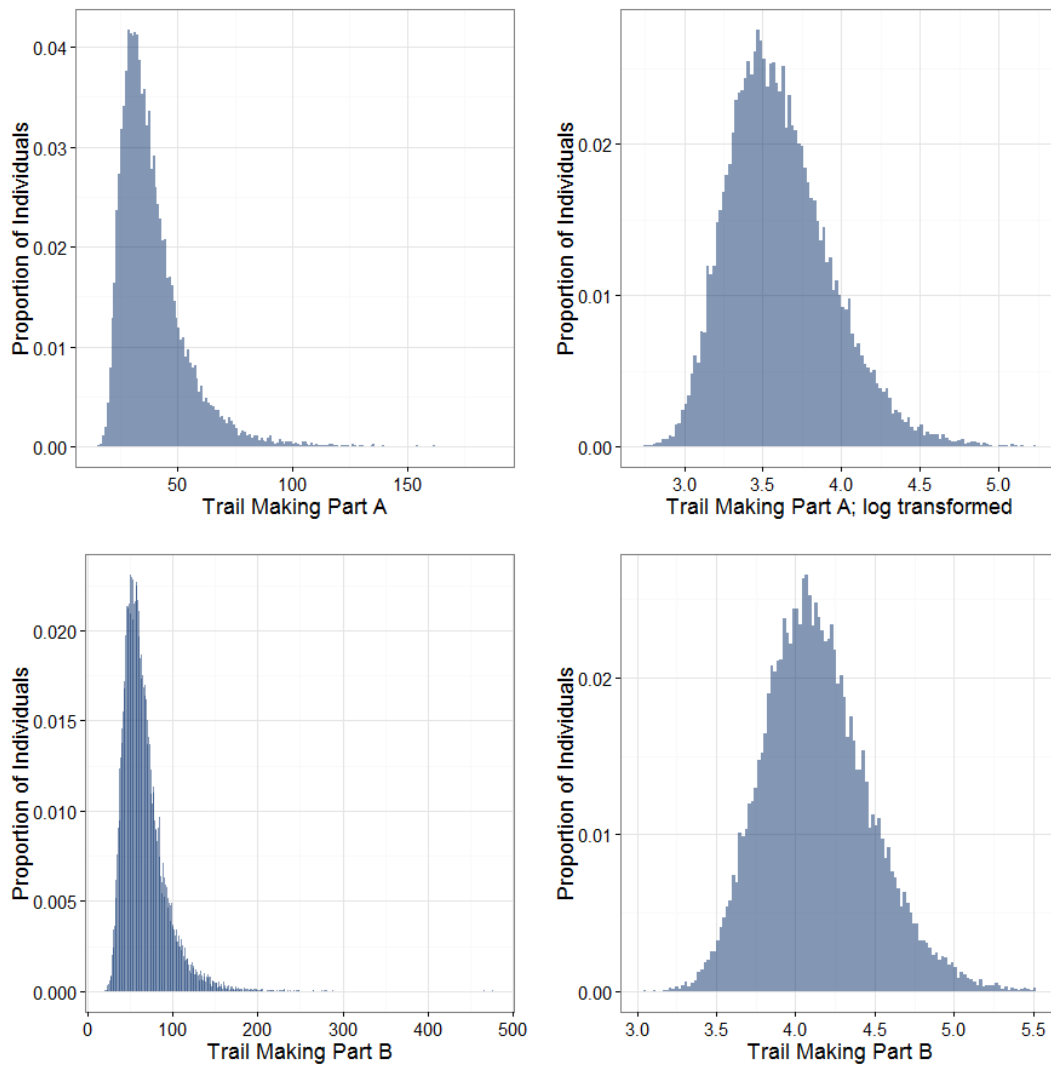


Figure 3-17. Distributions of Trail Making Part A (top) and Trail Making Part B (bottom) scores; left, untransformed; right, transformed and outliers excluded.

Both TMT measures showed a stable decline with age, with little difference between males and females, as shown in Figure 3-18. The Townsend deprivation index distribution is shown in Figure 3-19, and shows no difference in TMT performance between males and females across the distribution of the Townsend deprivation index scores. Figure 3-20 shows that individuals with more qualifications have better TMT performance. A total of 23,822 individuals with genetic data completed the TMT A task, and 23,812 individuals with genetic data completed the TMT B task.

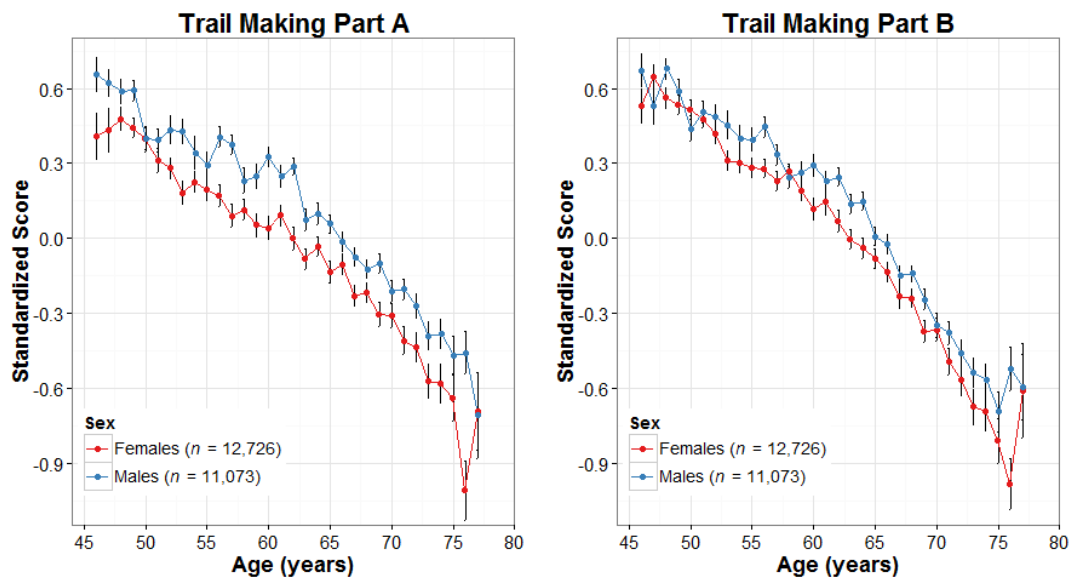


Figure 3-18. Age distribution for TMT A (left) and TMT B (right) separated by sex. Error bars represent +/- one standard error of the mean.

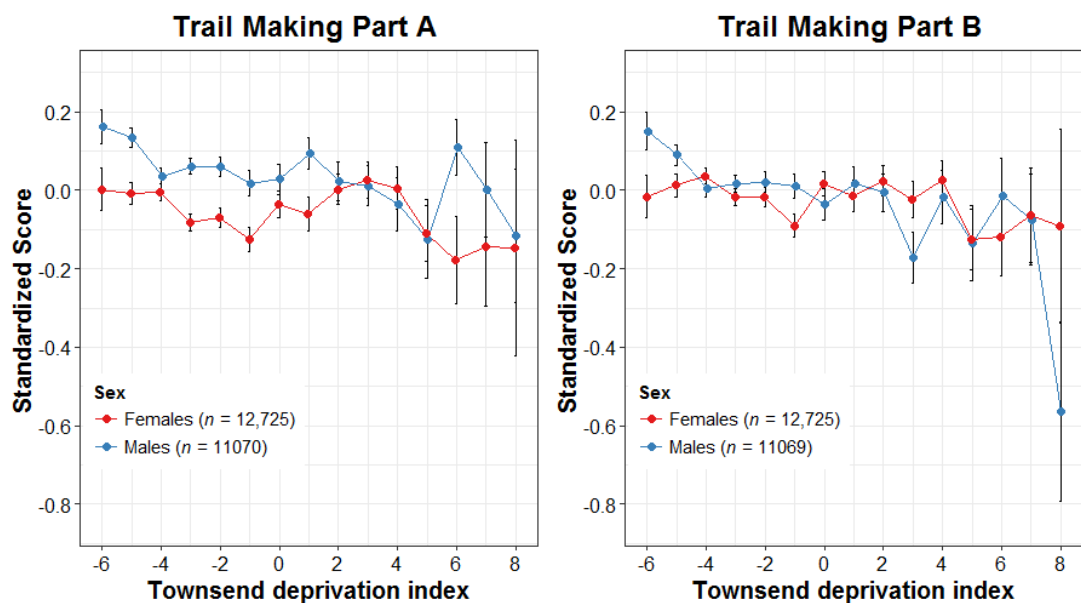


Figure 3-19. Townsend deprivation index distribution for TMT A (left) and TMT B (right) separated by sex. Error bars represent +/- one standard error of the mean. Individuals with a Townsend deprivation index > 8 are not displayed in the graph due to the low N.

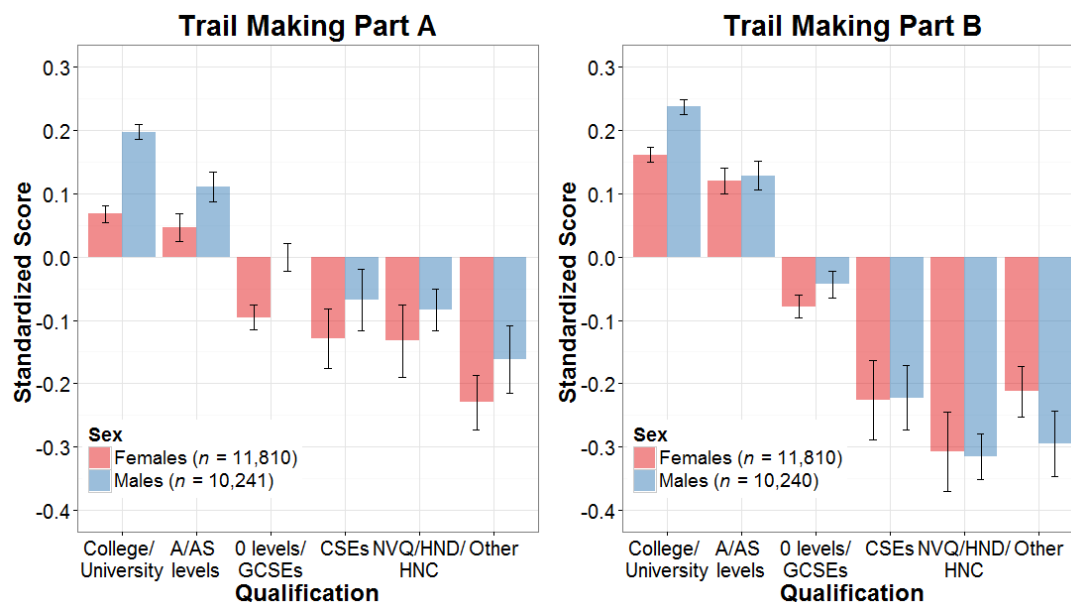


Figure 3-20. Qualifications distribution for TMT A (left) and TMT B (right) separated by sex. Error bars represent +/- one standard error of the mean.

3.4. Negative emotions

3.4.1. Neuroticism

Neuroticism is the personality trait that assesses individual differences in the tendency to experience negative emotions. This trait was measured, at baseline, by the Neuroticism scale of the Eysenck Personality Questionnaire Short Form-Revised (S. B. G. Eysenck, Eysenck, & Barrett, 1985), consisting of the following 12 yes (scored as 1) or no (scored as 0) items; "Does your mood often go up and down?"; "Do you ever feel 'just miserable' for no reason?"; "Are you an irritable person?"; "Are your feelings easily hurt?"; "Do you often feel 'fed-up'?"; "Would you call yourself a nervous person?"; "Are you a worrier?"; "Would you call yourself tense or 'highly strung'?"; "Do you worry too long after an embarrassing experience?"; "Do you suffer from 'nerves'?"; "Do you often feel lonely?"; "Are you often troubled by feelings of guilt?". The neuroticism score was calculated as the total of the twelve items, thus ranging from 0 – 12 (Gale et al., 2016; D. J. Smith et al., 2013). The neuroticism scores are not normally distributed, and show a zero-inflation, as shown in Figure 3-21. No transformation was performed for the neuroticism scores.

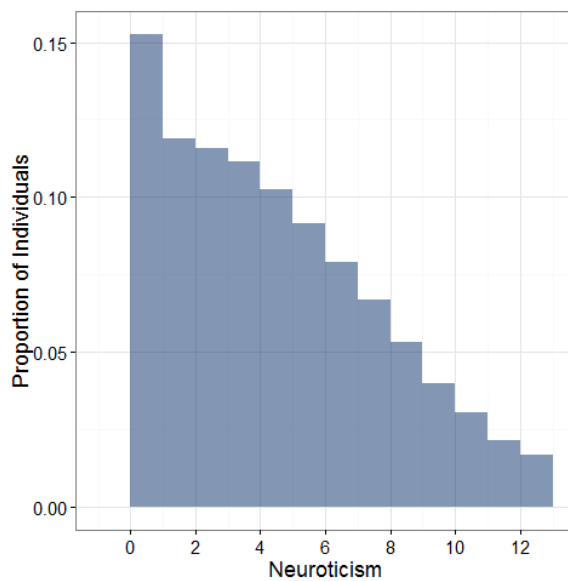


Figure 3-21. Distribution of neuroticism scores in UK Biobank.

The neuroticism scale shows a reliability of above 0.8 (S. B. G. Eysenck et al., 1985) and has been validated in older individuals, showing a correlation of -0.84 with the International Personality Item Pool (IPIP) – Emotional Stability scale and of 0.85 with the NEO-Five Factor Inventory (NEO-FFI) – Neuroticism Scale, two of the most widely used neuroticism scales (Gow, Whiteman, Pattie, & Deary, 2005). Figure 3-22 shows that neuroticism declines with both older age and better socio-economic status (lower Townsend deprivation index). Females score consistently higher than males on neuroticism, as previously shown by Soto et al. (2011). Individuals with higher educational attainment score lower on neuroticism (Figure 3-23). A total of 108,038 individuals with genetic data completed the neuroticism questionnaire.

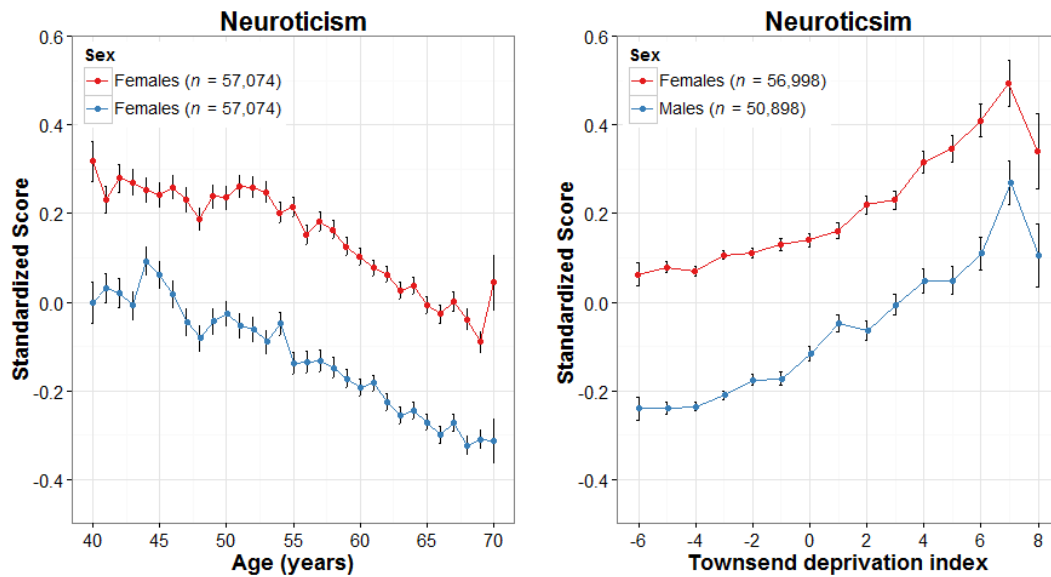


Figure 3-22. Age (left) and Townsend deprivation index (right) mean and standard error scores for neuroticism separated by sex. Error bars represent \pm one standard error of the mean. Individuals with a Townsend deprivation index > 8 are not displayed in the graph due to the low N.

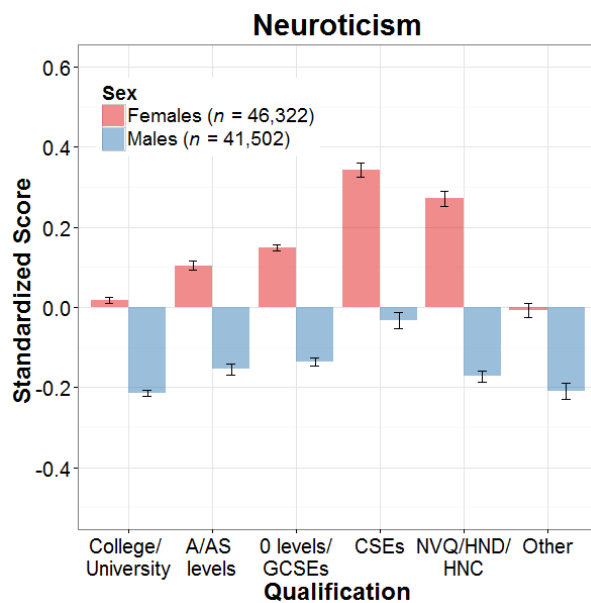


Figure 3-23. Qualifications distribution for neuroticism separated by sex. Error bars represent \pm one standard error of the mean.

3.4.2. Self-reported tiredness

At baseline, participants were asked the question, "Over the past two weeks, how often have you felt tired or had little energy?" Possible answers were: "Not at all/Several days/More than half the day/Nearly every day/Do not know/Prefer not to answer". This question was asked as part of the Mental Health Questionnaire, which consists of items from the Patient Health Questionnaire (Spitzer, Kroenke, & Williams, 1999). Participants answering with "Do not know" or "Prefer not to answer" were excluded, resulting in a four-category variable for tiredness ranging from "Not at all" to "Nearly every day". A total of 108,976 individuals with genetic data answered the tiredness question. Table 3-3 shows the number of individuals in each category of tiredness.

Table 3-3. Distribution of self-reported tiredness in UK Biobank.

	Number of individuals (%)
Not at all	51 416 (47.2)
Several days	44 208 (40.6)
More than half the days	6404 (5.9)
Nearly every day	6948 (6.4)

Figure 3-24 shows that tiredness, when treated as a continuous trait, decreases with age, and that females reported to be more tired than males. As shown in Figure 3-25 the percentage of individuals reporting they were not tired at all increases with age, whereas increasing Townsend deprivation index, i.e. lower socioeconomic status, was associated with individuals reporting they were more tired. Very little differences is shown for different categories of educational attainment (Figure 3-26).

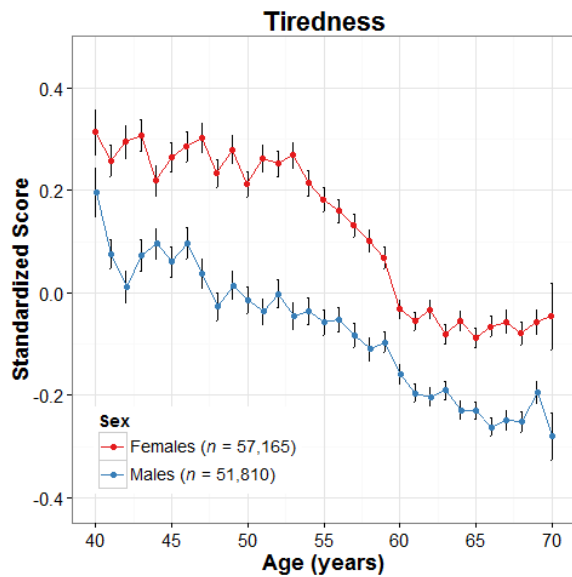


Figure 3-24. Age- and sex distribution of self-reported tiredness as a continuous variable. Error bars represent +/- one standard error of the mean.

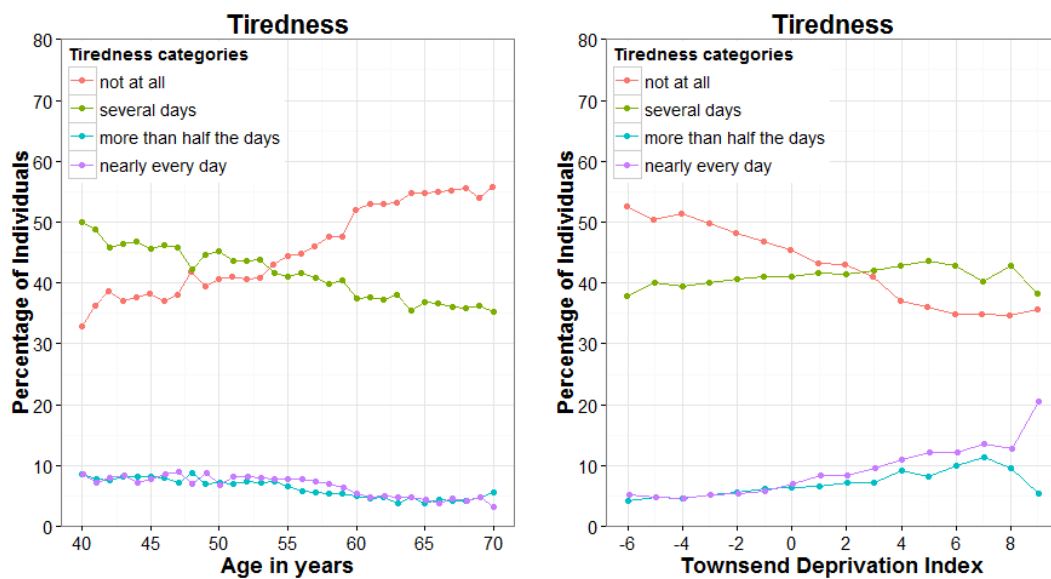


Figure 3-25. Age (left) and Townsend deprivation index (right) distribution for self-reported tiredness. Individuals with a Townsend deprivation index > 9 are not displayed in the graph due to the low N.

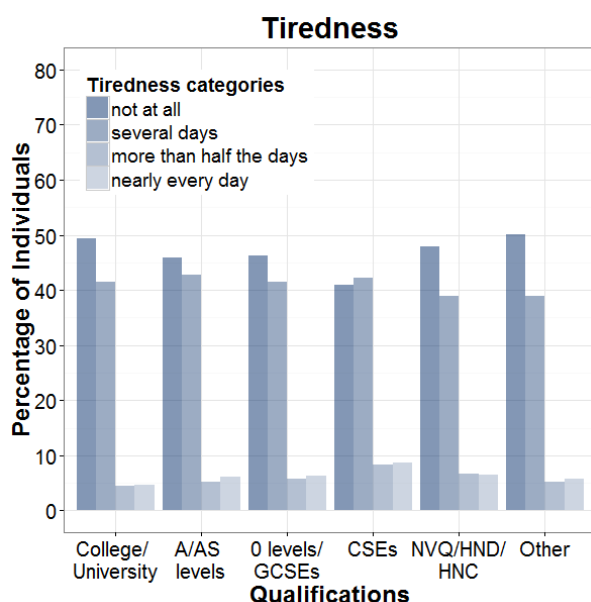


Figure 3-26. Distribution of each category of tiredness for each category of educational attainment, shown as percentage of individuals in each group.

3.5. Genotypic data

3.5.1. DNA extraction and genotyping

DNA was extracted from blood samples of 152,279 UK Biobank participants and genotyped for the interim release of the data, using either the UK BiLEVE array (N = 49,979) (Wain et al., 2015) or the UK Biobank Axiom array (N = 102,750). The UK BiLEVE array was designed for optimal imputation of markers associated with lung health and disease. This array formed the basis of the UK Biobank Axiom array, for which markers associated with a wide range of phenotypes have been added. The two arrays have an overlap of more than 95% and are very similar in processing stages.

DNA extraction took place at the UK Biobank facility in Stockport. Due to the large sample size, a sample selection algorithm ensured an equal distribution of assessment centres in each plate (UK Biobank, 2015c). Several quality checks were performed to ensure the quality of the extracted DNA (UK Biobank, 2014). All samples (UK BiLEVE array and UK Biobank Axiom array) were genotyped at the Affymetrix Research Services Laboratory in Santa Clara,

California, USA. Two controls from the 1000 Genomes were added to each plate containing 94 UK Biobank samples, to check for both control concordance with 1000 Genomes, as well as sample reproducibility. Genotypes were called in batches of around 4800 samples using the Affymetrix Power Tools Software and the Affymetrix Best Practices Workflow (Affymetrix, 2014). Quality control was performed by Affymetrix for each batch separately after genotype calling (Affymetrix, 2014, 2015). SNPs that did not meet the quality control thresholds set by Affymetrix were set to missing in all samples in that batch.

3.5.2. Quality control (QC)

Further sample quality control was performed (Hagenaars et al., 2016b). Samples were set to missing in all batches when the SNPs showed less reliable genotyping results, e.g. batch effects, Hardy-Weinberg equilibrium or SNPs that did not pass QC thresholds, based on Affymetrix recommendations, in all batches of the interim release (UK Biobank, 2015b). Samples were excluded in the order as displayed in Table 3-4, if they did not pass the following criteria:

Table 3-4. Sample quality control in UK Biobank.

Quality control criteria		Number of individuals removed
1	Non-White British ancestry (self-report)	32,484
2	Missingness	0
3	Relatedness (KING estimated kinship coefficient > 0.0442)	7948
4	QC failure in UK BiLEVE sample	187
5	Gender mismatch	0

Non-autosomal variants and SNPs with a minor allele frequency < 1% across all batches were removed prior to analysis. This resulted in a total sample of 112,151 individuals of the interim release for further analysis.

3.5.3. Imputation

UK Biobank performed genotype imputation on the genotype data in two steps; pre-phasing and imputation (UK Biobank, 2015a). Pre-phasing was done using a new version of SHAPEIT2 to allow for the large sample size of UK Biobank in chunks of 5000 SNPS with a 250 SNP overlap between chunks. The 1000 Genomes phase 3 and UK10K haplotype reference panels were merged in IMPUTE2 to get a large number of British and European ancestry haplotypes, as well as a set of various worldwide ancestry haplotypes, leading to a reference panel with 87,696,88 bi-allelic variants and 12,570 haplotypes. Whole genome imputation was carried out in 2Mb chunks with a 250 Kb buffer region, using IMPUTE2. Minor allele frequencies and imputation information scores were calculated for each SNP using QCTOOL.

3.6. Summary

This Chapter has described the recruitment procedures and measurements of UK Biobank. After quality control, a total sample of 112,151 individuals remained for further analysis, the actual numbers for each analysis will differ for each phenotype as displayed in Table 3-5. Participants were assessed on different cognitive abilities and filled in questionnaires about their mental health.

Table 3-5. Overview of UK Biobank measurements between the full sample and the genetic interim release after quality control (QC). SD, standard deviation; NA, not applicable.

Test	Assessment		full		Mean (SD)		Sex		Genetic		Mean (SD)		Sex		(%	
	year	N	sample				female)	QC					female)			(%
Reaction time	2006 - 2010	496811		559.64	54.43	111483	555.07				52.54					
				(118.00)			(112.62)									
Memory	2006 - 2010	498025		4.15 (3.40)	54.41	112067	4.06 (3.21)				52.49					
Verbal-numerical reasoning	2009 - 2010	165495		5.98 (2.16)	54.50	36035	6.16 (2.10)				52.09					
Educational attainment	2007 - 2010	492513		32.73%	54.44	111114	30.47%				52.55					
				degree			degree									
Trail making Part A	2014 - 2015	104059		39.19 (15.00)	55.08	23822	39.11 (14.73)				53.48					
Trail making Part B	2014 - 2015	104057		66.80 (25.75)	55.08	23812	66.44 (24.89)				53.48					
Neuroticism	2006 - 2010	479825		4.03 (3.18)	54.75	108038	4.02 (3.19)				52.83					
Self-reported tiredness	2006 - 2010	485396		NA	54.34	108976	NA				52.46					

4. Genetic overlap between cognitive ability and health

4.1. Introduction

Chapter 1 described the associations between general cognitive ability and health. Higher childhood cognitive ability is predictive of later mortality and less morbidity in later life, but morbidities, such as cardiovascular- and mental health diseases, are linked to a decline in cognitive ability. This indicates that cognitive ability and health are inextricably linked throughout life. Both cognitive ability and health outcomes are influenced by genetic factors to some extent, as shown by both behavioural and molecular genetic studies, discussed in Section 1.3.2.4 (G. Davies et al., 2016b; Ge, Chen, Neale, Sabuncu, & Smoller, 2016; Pickrell et al., 2016; Polderman et al., 2015). The genetic association between cognitive ability and health is not as well established, but some studies have indicated a shared genetic aetiology between cognitive ability and health outcomes (Arden et al., 2016; Brendan K. Bulik-Sullivan et al., 2015a; Hagenaars et al., 2016a; Harris et al., 2016a). In order to better understand the shared genetic aetiology between cognitive ability and health, it is important to also examine the causality of this correlation. The main limitation of previous molecular genetic studies, particularly when using a polygenic profile score approach, is a lack of power due to small sample sizes. The large sample size of UK Biobank overcomes this limitation and has enough statistical power to detect the usually small effects of polygenic associations. This Chapter first examines the shared genetic aetiology of verbal-numerical reasoning, reaction time, memory, and educational attainment with vascular-metabolic disease, psychiatric disorders, brain measures, physical and physiological measures, and life course cognitive traits and proxies. This study has been published in *Molecular Psychiatry* and this paper is included in full in Section 4.2. A more detailed description of the methodology used in this paper can be found in Section 1.3. The second part of this Chapter will use Mendelian randomization analysis to better understand the direction of effect between cognitive ability, educational

attainment, and physical health measures. This study has been accepted for publication in *Scientific Reports* and is included in full in Section 4.3.

4.2. Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112,151) and 24 GWAS consortia.

ORIGINAL ARTICLE

Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank ($N=112\,151$) and 24 GWAS consortia

SP Hagenaars^{1,2,3,13}, SE Harris^{1,4,13}, G Davies^{1,2}, WD Hill^{1,2}, DCM Liewald^{1,2}, SJ Ritchie^{1,2}, RE Marioni^{1,4,5}, C Fawns-Ritchie^{1,2}, B Cullen⁶, R Malik⁷, METASTROKE Consortium, International Consortium for Blood Pressure GWAS, SpiroMeta Consortium, CHARGE Consortium Pulmonary Group, CHARGE Consortium Aging and Longevity Group, BB Worrall^{8,9}, CLM Sudlow^{1,4,10}, JM Wardlaw^{1,10}, J Gallacher¹¹, J Pell⁶, AM McIntosh³, DJ Smith⁶, CR Gale^{1,2,12,14} and IJ Deary^{1,2,14}

Causes of the well-documented association between low levels of cognitive functioning and many adverse neuropsychiatric outcomes, poorer physical health and earlier death remain unknown. We used linkage disequilibrium regression and polygenic profile scoring to test for shared genetic aetiology between cognitive functions and neuropsychiatric disorders and physical health. Using information provided by many published genome-wide association study consortia, we created polygenic profile scores for 24 vascular–metabolic, neuropsychiatric, physiological–anthropometric and cognitive traits in the participants of UK Biobank, a very large population-based sample ($N=112\,151$). Pleiotropy between cognitive and health traits was quantified by deriving genetic correlations using summary genome-wide association study statistics and to the method of linkage disequilibrium score regression. Substantial and significant genetic correlations were observed between cognitive test scores in the UK Biobank sample and many of the mental and physical health-related traits and disorders assessed here. In addition, highly significant associations were observed between the cognitive test scores in the UK Biobank sample and many polygenic profile scores, including coronary artery disease, stroke, Alzheimer's disease, schizophrenia, autism, major depressive disorder, body mass index, intracranial volume, infant head circumference and childhood cognitive ability. Where disease diagnosis was available for UK Biobank participants, we were able to show that these results were not confounded by those who had the relevant disease. These findings indicate that a substantial level of pleiotropy exists between cognitive abilities and many human mental and physical health disorders and traits and that it can be used to predict phenotypic variance across samples.

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INTRODUCTION

Cognitive functioning is positively associated with greater longevity and less physical and psychiatric morbidity, and negatively associated with many quantitative disease risk factors and indices.¹ Some specific associations between cognitive functions and health appear to arise because an illness has lowered prior levels of cognitive function.^{2,3} For others, the direction of causation appears to be the reverse: there are many examples of associations between lower cognitive functions in youth, even childhood, and higher risk of later mental and physical illness and earlier death.^{4–8} In some cases, it is not clear whether illness affects cognitive functioning or vice versa, or whether both are influenced by some common factors. Many examples of these phenotypic and cognitive–illness associations are shown in

Supplementary Table 1. Overall, the causes of these cognitive–health associations remain unknown and warrant further investigation. It is also well recognized that lower educational attainment is associated with adverse health outcomes,⁹ and educational attainment has been used as a successful proxy for cognitive ability in genetic research.^{10,11} A study that included three cohorts of twins indicated that the association between higher cognitive function and increased lifespan was mostly owing to common genetic effects.¹²

The associations between cognitive and health and illness variables may, in part, reflect shared genetic influences. Cognitive functions show moderate heritability,¹³ and so do many physical and mental illnesses and health-associated anthropometric measures.¹⁴ Therefore, researchers have begun to examine

¹Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK; ²Department of Psychology, University of Edinburgh, Edinburgh, UK; ³Division of Psychiatry, University of Edinburgh, Edinburgh, UK; ⁴Medical Genetics Section, Centre for Genomic and Experimental Medicine, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, UK; ⁵Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia; ⁶Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK; ⁷Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians-Universität, Munich, Germany; ⁸Department of Neurology, University of Virginia, Charlottesville, VA, USA; ⁹Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA; ¹⁰Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK; ¹¹Department of Psychiatry, University of Oxford, Oxford, UK and ¹²MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK. Correspondence: Professor IJ Deary, Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh, Scotland EH8 9JZ, UK. E-mail: i.deary@ed.ac.uk

¹³These authors contributed equally to the work.

¹⁴These authors contributed equally to the work.

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pleiotropy between scores on tests of cognitive ability and health-related variables.^{15,16} Pleiotropy is the overlap between the genetic architecture of two or more traits, perhaps owing to a variety of shared causal pathways.¹⁷ Originally, the possibility of pleiotropy in cognitive–health associations was tested using family- and twin-based designs.¹⁸ However, now data from single-nucleotide polymorphism (SNP) genotyping can assess pleiotropy, opening the possibility for larger-scale, population-generalizable studies.

Multiple methods can be used to test for pleiotropy using SNP-based genetic data. Calculating genetic correlations between health measures using the summary results of previous genome-wide association studies (GWAS) has become possible using the method of linkage disequilibrium (LD) score regression.¹⁹ In addition, the method of polygenic profile scoring²⁰ also uses summary GWAS data to test whether genetic liability to a given illness or health-related anthropometric measurement is associated with phenotypes such as cognitive test scores in a second independent data set. For example, lower cognitive functioning was associated significantly in healthy older people with higher polygenic risk for schizophrenia²¹ and stroke,²² but not for dementia.²³ However, most polygenic profile studies to date have been limited in the information they provide on this important topic: they have reported on single health outcomes, and have used relatively small cohorts with available cognitive data. Two recent papers, using polygenic profile scoring and/or LD score regression, have identified pleiotropy between a number of health-related traits and diseases, and educational attainment¹⁵ and between a number of psychiatric disorders and cognitive traits, and behavioural traits.¹⁶

We aimed to discover whether cognitive functioning is associated with many physical and mental health and health-related anthropometric measurements, in part, because of their shared genetic aetiology using the recently released UK Biobank genetic data (<http://www.ukbiobank.ac.uk>).²⁴ We curated GWAS meta-analyses for 24 health-related measures, and used them in two complementary methods to test for cognitive–health pleiotropy. First, we used LD score regression to derive genetic correlations between cognitive function and educational attainment traits measured in UK Biobank, and 24 health-related measures from the GWAS meta-analyses. Second, to provide a measure of the phenotypic variance that these genetic correlations account for, the summary data from GWAS meta-analyses were used to calculate polygenic profile scores in UK Biobank, which includes cognitive, educational and genome-wide SNP data on over 110 000 individuals. We calculated the associations between polygenic profile scores for the 24 health-related measures and the cognitive domains of memory, processing speed and verbal-numerical reasoning, and educational attainment in UK Biobank participants. These new data and results provide a substantial advance in understanding the aetiology of cognitive–health associations.

MATERIALS AND METHODS

Study design and participants

This study includes baseline data from the UK Biobank Study (<http://www.ukbiobank.ac.uk>).²⁴ UK Biobank received ethical approval from the Research Ethics Committee. The Research Ethics Committee reference for UK Biobank is 11/NW/0382. UK Biobank is a health resource for researchers that aims to improve the prevention, diagnosis and treatment of a range of illnesses. A total 502 655 community-dwelling participants aged between 37 and 73 years were recruited between 2006 and 2010 in the United Kingdom. They underwent cognitive and physical assessments, provided blood, urine and saliva samples for future analysis, gave detailed information about their backgrounds and lifestyles, and agreed to have their health followed longitudinally. For the present study, genome-wide genotyping data were available on 112 151 individuals (58 914 females) aged 40–73 years (mean age = 56.9 years, s.d. = 7.9) after the quality control process (see below).

Procedures

Cognitive phenotypes. Three cognitive tests were used in the present study. These tests, which cover three important cognitive domains, were reaction time ($n=496\,891$; of whom 111 484 also had genotyping data), memory ($n=498\,486$; 112 067 with genotyping) and verbal-numerical reasoning ($n=180\,919$; 36 035 with genotyping). The reaction time test was a computerized ‘Snap’ game, in which participants were to press a button as quickly as possible when two ‘cards’ on screen were matching. There were eight experimental trials, with a Cronbach α reliability of 0.85. In the memory test, participants were shown a set of 12 cards (six pairs) on a computer screen for 5 s, and had to recall which were matching after the cards had been obscured. We used the number of errors in this task as the (inverse) measure of memory ability. The verbal-numerical reasoning task involved a series of 13 items assessing verbal and arithmetical deduction (Cronbach α reliability = 0.62). A total 492 513 participants also reported whether or not they had a college or university degree (henceforth referred to as ‘educational attainment’), 111 114 of whom had genotyping data. Full details on the content and administration of each test (and the educational attainment question) are provided in the Supplementary Materials. Supplementary Figure 1 shows that the broad age distribution of the cognitive tests did not differ between the full and genotyped samples.

Genotyping and quality control. A total 152 729 UK Biobank blood samples were genotyped using either the UK BiLEVE array ($N=49\,979$)²⁵ or the UK Biobank axiom array ($N=102\,750$). Details of the array design, genotyping, quality control and imputation are available in a publication²⁵ and in the Supplementary Materials. Quality control was performed by Affymetrix, the Wellcome Trust Centre for Human Genetics, and by the present authors; this included removal of participants based on missingness, relatedness, gender mismatch, non-British ancestry and other criteria, and is described in the Supplementary Materials.

GWAS analyses in the UK Biobank sample. GWAS analyses were performed on the three UK Biobank cognitive test scores and on the Educational Attainment data to use the summary results for LD score regression. Details of the GWAS procedures are provided in the Supplementary Materials.

Curation of summary results from GWAS consortia on health-related variables. To conduct LD score regression and polygenic profile score analyses between the UK Biobank cognitive data and the genetic predisposition to a large number of health-related variables, selected because of previous associations with cognitive functions (Supplementary Table 1), we gathered 24 sets of summary results from international GWAS consortia. Details of the health-related variables, the consortia’s websites, key references and number of subjects included in each consortia’s GWAS are given in Supplementary Table 2.

Statistical analysis

Computing genetic associations between health and cognitive variables. We used two methods to compute genetic associations between health variables from 24 GWAS consortia, and cognitive and educational attainment variables measured in UK Biobank: LD score regression and polygenic profile scoring. Each provides a different metric to infer the existence of pleiotropy between pairs of traits. LD score regression was used to derive genetic correlations to determine the degree to which the polygenic architecture of a trait overlaps with that of another. Next, the polygenic profile score method was used to test the extent to which these genetic correlations are predictive of phenotypic variance across samples. Both LD score regression and polygenic profile scores are dependent on the traits analysed being highly polygenic in nature, that is, where a large number of variants of small effect contribute toward phenotypic variation.^{19,20} This was tested for each trait before running the LD score regression and polygenic profile analyses.

LD score regression. To quantify the level of pleiotropy between the traits assessed here, LD score regression was used.^{15,19} LD score regression is a class of techniques that exploits the correlational structure of the SNPs found across the genome. In the Supplementary Materials, we provide more details of LD score regression. Here, we use LD score regression to derive genetic correlations between health-related and cognitive traits using 24 large GWAS consortia data sets that enable pleiotropy of their health-related traits to be quantified with the cognitive traits in UK Biobank. We followed the data processing pipeline devised by Bulik-Sullivan *et al.*,¹⁹ described in more detail in the Supplementary Materials. To ensure that the

Table 1. Descriptive statistics and phenotypic (below diagonal) and genetic (above diagonal) correlations for the UK Biobank cognitive and educational variables in all genotyped participants

Variable	Mean (s.d.)	Genetic/phenotypic correlation			
		Reaction time	Memory	Verbal-numerical reasoning	Educational attainment
Reaction time (ms)	555.08 (112.69)	—	0.179 (0.06)*	0.206 (0.05)*	0.066 (0.04)
Memory (errors)	4.06 (3.23)	0.116 (0.003)*	—	0.437 (0.06)*	0.126 (0.05) [†]
Verbal-numerical reasoning (max. score 13)	6.16 (2.10)	0.156 (0.005)*	0.176 (0.005)*	—	0.729 (0.04)*
Educational attainment	30.5% with degree	0.099 (0.003)*	0.052 (0.003)*	0.338 (0.005)*	—

Genetic correlations are based on the results of genome-wide association studies of the UK Biobank variables. Standard errors for the correlations are shown in parentheses. For the phenotypic variables, Pearson correlations used for continuous–continuous correlations and point–biseal correlations for continuous–categorical correlations. All variables are coded such that higher scores indicate better performance. * P -value < 0.0001; [†] P -value < 0.05.

genetic correlation for the Alzheimer's disease phenotype was not driven by a single locus or biased the fit of the regression model, a 500 kb region centred on the *APOE* locus was removed and this phenotype was re-run. This additional model is referred to in the tables and figures below as 'Alzheimer's disease (500 kb)'.

Polygenic profiling. The UK Biobank genotyping data required recoding from numeric (1, 2) allele coding to standard ACGT format before being used in polygenic profile scoring analyses. This was achieved using a bespoke programme developed by one of the present authors (DCML), details of which are provided in the Supplementary Materials.

Polygenic profiles were created for 24 health-related phenotypes (see Table 3, and Supplementary Table 1) in all genotyped participants using PRSice.²⁶ PRSice calculates the sum of alleles associated with the phenotype of interest across many genetic loci, weighted by their effect sizes estimated from a GWAS of that phenotype in an independent sample. Before creating the scores, SNPs with a minor allele frequency < 0.01 were removed and clumping was used to obtain SNPs in linkage equilibrium with an r^2 < 0.25 within a 200 bp window. Multiple scores were then created for each phenotype containing SNPs selected according to the significance of their association with the phenotype. The GWAS summary data for each of the 24 health-related phenotypes were used to create five polygenic profiles in the UK Biobank participants, at thresholds of P < 0.01, P < 0.05, P < 0.1, P < 0.5 and all SNPs.

Correlation coefficients were calculated between each of the UK Biobank cognitive phenotypes. The associations between the polygenic profiles and the target phenotype were examined in regression models (linear regression for the continuous cognitive traits and logistic regression for the binary education variable), adjusting for age at measurement, sex, genotyping batch and array, assessment centre and the first 10 genetic principal components to adjust for population stratification. We corrected for multiple testing across all polygenic profile scores at all significance thresholds for associations with all cognitive phenotypes (470 tests) using the false discovery rate method.²⁷ We conducted sensitivity analyses as follows. Where the original findings were false discovery rate significant, UK Biobank participants with cardiovascular disease (N = 5300) were then removed from analyses of coronary artery disease, those with diabetes (N = 5800) were removed from type 2 diabetes analyses, and those with hypertension (N = 26 912) were removed from systolic blood pressure analyses. See Supplementary Materials for further details of these sensitivity analysis. Four multivariate regression models were then performed, including all 24 polygenic profile scores and the covariates described above.

RESULTS

Phenotypic and genetic associations among the UK Biobank's cognitive traits

In addition to descriptive statistics, Table 1 shows phenotypic correlations and genetic correlations (calculated using LD score regression) among the cognitive traits in UK Biobank. There were modest correlations between the three cognitive test scores; those who did well on one test tended to do well on the other two. Verbal-numerical reasoning showed the highest phenotypic

correlation with educational attainment (r = 0.30). The strongest genetic correlation was also between verbal-numerical reasoning and educational attainment (r_g = 0.79). All but one of the other genetic correlations were statistically significant: there was a nonsignificant genetic correlation between educational attainment and reaction time. These results show that different cognitive traits and educational attainment correlate, in part, due to overlapping genetic architecture.

Cognitive–health pleiotropy: overview

To test for pleiotropy between cognitive and health traits, we present the LD score regression (Table 2, Figure 1) and polygenic profile score (Table 3, Supplementary Tables 4a and d) results for the four UK Biobank cognitive function and educational attainment traits, and the 24 health-related traits from GWAS consortia. Results are false discovery rate-corrected for multiple comparisons.

In overview, using LD score regression results, educational attainment showed significant genetic correlations with 14 of the 22 health-related traits, verbal-numerical reasoning had significant genetic correlations with 10 of the 24, and memory and reaction time both correlated significantly with 3 of the 24 (Table 2, Figure 1).

In the polygenic profile score results, using the best SNP threshold of the five that were created, summary GWAS data from 19 of 22 consortia predicted significant phenotypic variation in educational attainment in the UK Biobank sample (Table 3). For verbal-numerical reasoning, results from 15 of the 24 consortia predicted significant phenotypic variation. The numbers for memory and reaction time were seven and six, respectively. The numbers of SNPs included in each polygenic threshold score for each of the 24 health-related traits are shown in Supplementary Table 3. The fuller results relating all five of the SNP thresholds for all the 24 health-associated variables with the UK Biobank cognitive phenotypes are shown in Supplementary Tables 4a–d.

Cognitive–health pleiotropy: brain-cognitive traits

Cognitive and brain traits provided a first check before moving to more mainstream health measures whose phenotypes appear more distant from cognitive function. In LD score regression analyses, we expected significant genetic correlations between GWAS consortia results from cognitive- and brain-related traits and the UK Biobank GWAS results for cognitive variables. In polygenic risk score analyses, we expected the polygenic scores based on the health-related GWAS consortia's results to predict phenotypic variation in UK Biobank's cognitive traits.

Using LD score regression, genetic correlations of greater than 0.9 were found between UK Biobank's Education Attainment variable and GWAS consortia results from childhood cognitive

Table 2. Genetic correlations between the cognitive and education phenotypes documented in the UK Biobank data set and the health-related variables collected from GWAS consortia

Health-related variables from GWAS consortia	Verbal-numerical reasoning (n = 36 035)			Reaction time (n = 111 484)			Memory (n = 112 067)			Educational attainment (n = 111 114)		
	r_g	s.e.	P	r_g	s.e.	P	r_g	s.e.	P	r_g	s.e.	P
<i>Vascular-metabolic diseases</i>												
Coronary artery disease	-0.086	0.062	0.163	0.058	0.066	0.378	0.058	0.074	0.430	-0.262	0.048	5.6×10^{-8}
Stroke: ischaemic	-0.231	0.092	0.012	-0.007	0.088	0.935	0.035	0.095	0.711	-0.168	0.066	0.011
Stroke: cardioembolic	-0.037	0.133	0.781	-0.104	0.125	0.405	-0.056	0.134	0.679	-0.027	0.092	0.771
Stroke: large vessel disease	-0.408	0.187	0.029	-0.061	0.156	0.695	0.010	0.172	0.953	-0.336	0.145	0.020
Stroke: small vessel disease	—	—	—	—	—	—	—	—	—	—	—	—
Type 2 diabetes	-0.023	0.064	0.725	0.034	0.064	0.590	0.059	0.077	0.444	-0.090	0.050	0.074
<i>Neuropsychiatric disorders</i>												
ADHD	-0.334	0.147	0.023	-0.072	0.138	0.599	-0.043	0.159	0.788	-0.305	0.141	0.030
Alzheimer's disease	-0.394	0.124	0.002	0.042	0.085	0.622	-0.131	0.116	0.256	-0.266	0.082	0.001
Alzheimer's disease (500 kb)	-0.325	0.081	6.0×10^{-5}	0.036	0.070	0.603	-0.117	0.097	0.229	-0.223	0.057	1.0×10^{-4}
Autism	0.187	0.066	0.005	-0.160	0.067	0.016	-0.092	0.081	0.258	0.344	0.053	6.7×10^{-11}
Bipolar disorder	-0.107	0.063	0.091	-0.131	0.066	0.048	-0.237	0.073	0.001	0.219	0.047	4.0×10^{-6}
Major depressive disorder	-0.108	0.093	0.248	-0.248	0.087	0.004	-0.217	0.106	0.042	-0.103	0.082	0.213
Schizophrenia	-0.295	0.045	3.5×10^{-11}	-0.240	0.040	2.1×10^{-9}	-0.339	0.041	1.1×10^{-16}	0.128	0.034	1.1×10^{-16}
<i>Brain measures</i>												
Hippocampal volume	-0.040	0.107	0.710	0.222	0.124	0.073	0.014	0.132	0.916	-0.076	0.086	0.380
Intracranial volume	0.245	0.101	0.015	-0.175	0.098	0.073	0.084	0.114	0.463	0.442	0.084	2.0×10^{-4}
Infant head circumference	0.193	0.093	0.038	-0.048	0.080	0.547	0.103	0.097	0.287	0.248	0.069	3.0×10^{-4}
<i>Physical and physiological measures</i>												
Blood pressure: diastolic	-0.071	0.057	0.213	-0.074	0.054	0.172	-0.050	0.065	0.442	-0.071	0.039	0.067
Blood pressure: systolic	-0.061	0.058	0.297	-0.027	0.052	0.600	-0.010	0.063	0.873	-0.082	0.037	0.026
BMI	-0.119	0.033	2.0×10^{-4}	-0.028	0.028	0.317	0.154	0.035	1.0×10^{-5}	-0.233	0.024	3.6×10^{-22}
Height	0.056	0.029	0.054	0.067	0.027	0.014	-0.017	0.033	0.609	0.120	0.024	5.0×10^{-7}
Longevity	0.111	0.092	0.226	-0.067	0.086	0.437	0.130	0.114	0.254	NA	NA	NA
Forced expiratory volume in 1 s (FEV ₁)	0.109	0.054	0.044	-0.061	0.048	0.209	-0.023	0.066	0.722	NA	NA	NA
<i>Life-course cognitive traits and proxies</i>												
Childhood cognitive ability	0.812	0.094	6.2×10^{-18}	0.067	0.089	0.451	0.100	0.112	0.370	0.906	0.082	4.2×10^{-28}
College degree	0.749	0.055	3.3×10^{-42}	0.046	0.053	0.388	-0.050	0.060	0.404	0.984	0.041	3.8×10^{-130}
Years of education	0.720	0.056	2.0×10^{-38}	0.031	0.048	0.523	-0.050	0.059	0.403	0.948	0.041	1.4×10^{-115}

Abbreviations: ADHD, attention deficit hyperactivity disorder; BMI, body mass index; GWAS, genome-wide association study; NA, not available; r_g , genetic correlation. Statistically significant P -values (after false discovery rate correction; threshold: $P < 0.016$) are shown in bold. There was no evidence for a sufficient polygenic signal in the small vessel disease data set and so no genetic correlation could be derived as shown in Supplementary Table 3.

ability, college degree attainment and years of education (Table 2, Figure 1). The genetic correlation between UK Biobank's Educational Attainment variable and ENIGMA's intracranial volume was 0.44 and with Early Growth Genetics Consortium's infant head circumference was 0.25. Verbal-numerical reasoning in UK Biobank had a genetic correlation of 0.81 with childhood cognitive ability, of 0.75 with attaining a college degree (Social Science Genetic Association Consortium), 0.72 with years of education (Social Science Genetic Association Consortium), and 0.25 with intracranial volume. These results demonstrate substantial shared genetic aetiology between brain size, cognitive ability and educational attainment. Reaction time and memory did not have significant genetic correlations with the brain, cognitive or educational variables.

In summarizing polygenic profile analyses' results in the text, we shall use standardized betas (β). Polygenic profiles for higher childhood cognitive ability and a higher level of educational attainment (Social Science Genetic Association Consortium) were significantly associated with increased likelihood of a college degree (β between 0.12 and 0.28), higher scores on verbal-numerical reasoning (β between 0.08 and 0.11), and faster reaction time (β about 0.001). Only childhood cognitive ability

was significantly associated with memory ($\beta = 0.01$). Polygenic profiles for greater intracranial volume and greater infant head circumference were significantly associated with increased likelihood of a college degree ($\beta = 0.04$ and 0.05 , respectively), and higher scores on verbal-numerical reasoning (both $\beta = 0.02$).

Cognitive-health pleiotropy: neuropsychiatric disorders

Using LD score regression, there were negative genetic correlations between Alzheimer's disease and UK Biobank's educational attainment variable and verbal-numerical reasoning (r_g between -0.27 and -0.39 ; Table 2, Figure 1). Autism had positive genetic correlations with the same two Biobank variables: 0.34 for educational attainment and 0.19 for verbal-numerical reasoning. Bipolar disorder and schizophrenia showed a pattern of having a positive genetic correlation with educational attainment (0.22 and 0.13, respectively) and a negative genetic correlation with verbal-numerical reasoning (-0.11 and -0.30 , respectively). Schizophrenia was genetically associated with slower reaction time (-0.24) and poorer memory (-0.34). Bipolar disorder was also genetically associated with poorer memory (-0.24). Major depressive disorder was genetically associated with slower reaction time (-0.25).

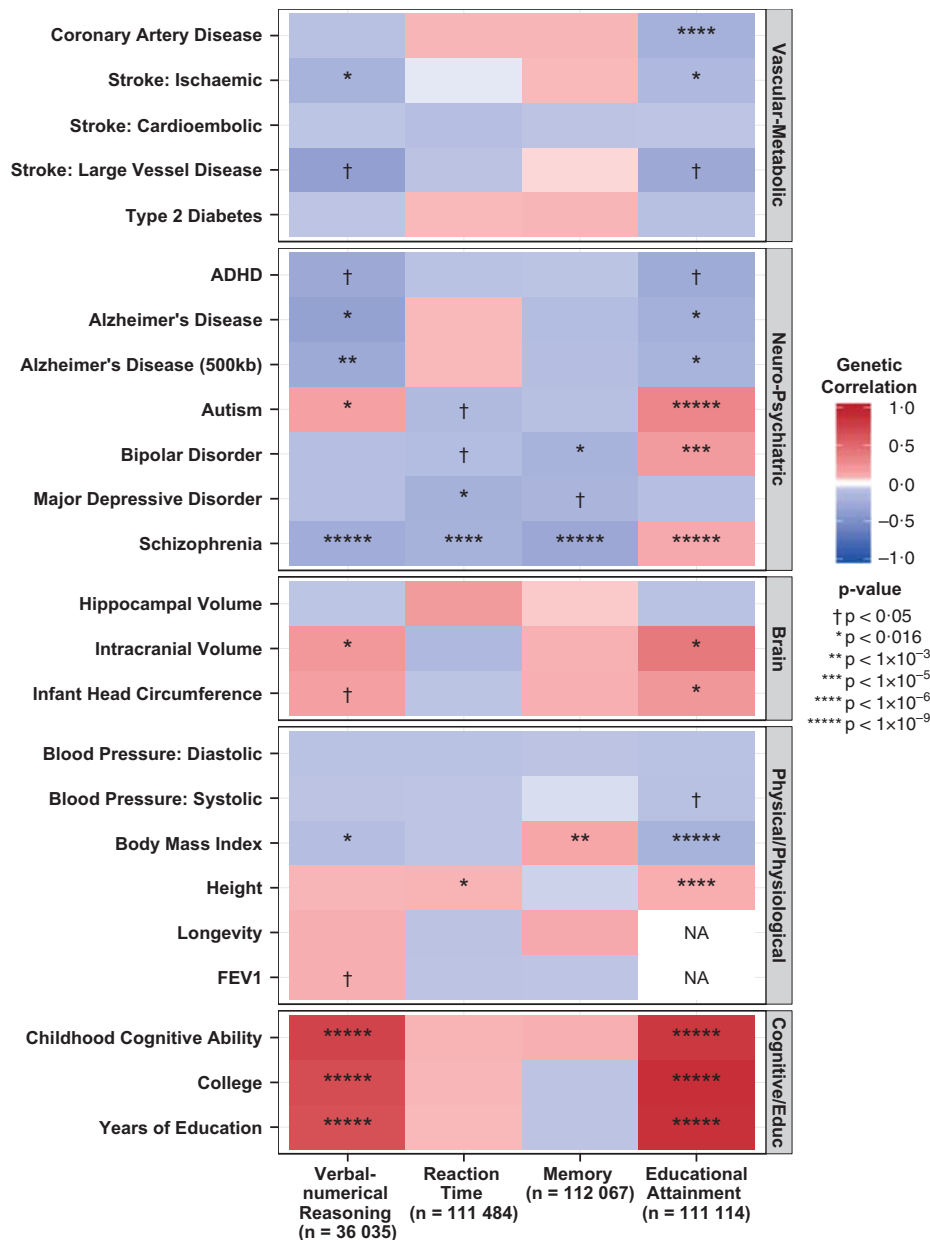


Figure 1. Heat map of genetic correlations calculated using LD regression between cognitive phenotypes in UK Biobank and health-related variables from GWAS consortia. Hues and colours depict, respectively, the strength and direction of the genetic correlation between the cognitive phenotypes in UK Biobank and the health-related variables. Red and blue indicate positive and negative correlations, respectively. Correlations with the darker shade associated with a stronger association. Based on results in Table 2. ADHD, attention deficit hyperactivity disorder; FEV₁, forced expiratory volume in 1 s; GWAS, genome-wide association study; LD, linkage disequilibrium; NA, not available.

Polygenic profile scoring replicated the directions of association found with LD score regression-estimated genetic correlations (Table 3). Higher polygenic risk for Alzheimer's disease was associated with lower educational attainment and a lower score on verbal-numerical reasoning and memory (β between -0.01 and -0.05). Higher polygenic risk for ADHD was associated with lower educational attainment ($\beta = -0.03$). Higher polygenic risk for autism was associated with higher educational attainment and better verbal-numerical reasoning ($\beta = 0.07$ and 0.02 , respectively). Higher polygenic risk for bipolar disorder and schizophrenia had a positive association with educational attainment ($\beta = 0.06$ and 0.03 , respectively), and the genetic risk for schizophrenia and major depressive disorder had a negative association with verbal-numerical reasoning ($\beta = -0.06$ and -0.02 , respectively).

Cognitive–health pleiotropy: vascular–metabolic diseases

There were significant negative genetic correlations between UK Biobank's educational attainment variable and coronary artery disease (-0.26), ischaemic stroke (-0.17) and large vessel disease stroke (-0.34 ; Table 2, Figure 1). There was a significant negative genetic correlation between ischaemic stroke and verbal-numerical reasoning (-0.23).

Greater polygenic risk for coronary artery disease, type 2 diabetes, and ischaemic, and large and small vessel disease stroke were all associated with lower educational attainment (β between -0.02 and -0.05). Greater polygenic risk for coronary artery disease, and ischaemic and large vessel disease stroke were associated with lower verbal-numerical reasoning scores

Table 3. Associations between polygenic profiles of health-related traits created from GWAS consortia summary data, and UK Biobank cognitive and education phenotypes controlling for age, sex, assessment centre, genotyping batch and array and 10 principal components for population structure

Health-related variables from GWAS consortia	Verbal-numerical reasoning (n = 36 035)			Reaction time (n = 111 484)			Memory (n = 112 067)			Educational attainment (n = 111 114)		
	Thresh	β	P	Thresh	β	P	Thresh	β	P	Thresh	β	P
Vascular-metabolic diseases												
Coronary artery disease	0.5	-0.019	0.0002^a	0.1	0.001	0.0875	0.1	-0.004	0.2265	1	-0.047	7.92 × 10^{-13b}
Stroke: ischaemic	0.05	-0.014	0.0068	0.01	-0.001	0.0791	0.01	-0.004	0.1759	0.5	-0.020	0.0026
Stroke: cardioembolic	1	-0.009	0.0937	0.01	0.001	0.0817	0.01	0.005	0.0638	0.5	-0.003	0.6931
Stroke: large vessel disease	0.01	-0.013	0.0155	0.05	2.26 × 10 ⁻⁴	0.6714	0.05	-0.008	0.0056	0.1	-0.031	5.31 × 10⁻⁶
Stroke: small vessel disease	0.05	-0.012	0.0250	1	-0.001	0.3188	1	-0.004	0.1388	0.1	-0.034	2.96 × 10⁻⁷
Type 2 diabetes	1	-0.006	0.2490	0.1	-4.50 × 10 ⁻⁴	0.3982	0.1	0.003	0.2614	0.5	-0.025	0.0002^c
Neuropsychiatric disorders												
ADHD	1	-0.008	0.1054	1	-0.001	0.2485	1	0.001	0.6520	1	-0.027	4.68 × 10⁻⁵
Alzheimer's disease	0.05	-0.023	1.27 × 10⁻⁵	0.5	-0.001	0.0516	0.5	-0.011	1.22 × 10⁻⁴	1	-0.046	2.33 × 10⁻¹²
Autism	1	0.023	1.43 × 10⁻⁵	0.1	0.001	0.1176	0.1	0.002	0.4385	0.5	0.068	5.00 × 10⁻²⁵
Bipolar disorder	0.01	-0.006	0.2695	0.01	-0.002	0.0007	0.01	-0.017	3.21 × 10⁻⁸	0.5	0.057	1.35 × 10⁻¹⁷
Major depressive disorder	1	-0.020	0.0002	0.1	-0.002	0.0005	0.1	-0.014	1.91 × 10⁻⁶	1	-0.009	0.1905
Schizophrenia	0.05	-0.062	7.73 × 10⁻³²	0.1	-0.006	1.88 × 10⁻²⁵	0.1	-0.039	4.49 × 10⁻³⁹	0.05	0.025	0.0002
Brain measures												
Hippocampal volume	0.01	0.005	0.3552	0.5	0.001	0.1144	0.5	-0.005	0.0848	0.5	0.007	0.2887
Intracranial volume	0.5	0.016	0.0021	0.01	0.001	0.3306	0.01	0.005	0.0778	1	0.043	2.91 × 10⁻¹⁰
Infant head circumference	0.5	0.024	8.53 × 10⁻⁶	0.01	-0.001	0.0468	0.01	0.005	0.0782	0.1	0.050	4.01 × 10⁻¹⁴
Physical and physiological measures												
Blood pressure: diastolic	0.05	0.004	0.5044	0.01	0.001	0.2325	0.01	-0.002	0.5342	0.1	-0.022	0.0011
Blood pressure: systolic	0.1	0.013	0.0116	0.5	-4.97 × 10 ⁻⁴	0.3460	0.5	-0.003	0.3149	0.1	-0.035	7.61 × 10^{-8d}
BMI	0.5	-0.027	3.34 × 10⁻⁷	0.01	3.96 × 10 ⁻⁴	0.4507	0.01	0.016	7.31 × 10⁻⁸	0.5	-0.093	6.40 × 10⁻⁴⁵
Height	1	0.021	9.23 × 10⁻⁵	0.5	4.46 × 10 ⁻⁴	0.4135	0.5	0.003	0.3579	1	0.070	2.95 × 10⁻²⁴
Longevity	0.01	0.004	0.4091	0.05	3.23 × 10 ⁻⁴	0.5426	0.05	0.006	0.0484	NA	NA	NA
Forced expiratory volume in 1 s (FEV ₁)	0.5	0.012	0.0220	0.05	-0.001	0.1302	0.05	-0.005	0.0840	NA	NA	NA
Life-course cognitive traits and proxies												
Childhood cognitive ability	1	0.079	3.49 × 10⁻⁵¹	0.5	0.002	0.0002	0.5	0.014	1.65 × 10⁻⁶	1	0.122	3.92 × 10⁻⁷⁵
College degree	0.5	0.102	3.19 × 10⁻⁸³	0.5	0.001	0.0133	0.5	-0.002	0.4688	0.5	0.280	0
Years of education	1	0.106	2.96 × 10⁻⁸⁹	0.1	0.001	0.0156	0.1	-0.004	0.1563	1	0.210	0

Abbreviations: ADHD, attention deficit hyperactivity disorder; BMI, body mass index; FDR, false discovery rate; GWAS, genome-wide association study; NA, not available. ^aExcluding individuals with cardiovascular disease $\beta = -0.018$, $P = 0.0007$. ^bExcluding individuals with cardiovascular disease $\beta = -0.044$, $P = 4.66 \times 10^{-11}$. ^cExcluding individuals with diabetes $\beta = -0.020$, $P = 0.0032$. ^dExcluding individuals with hypertension $\beta = -0.028$, $P = 0.00016$. FDR-corrected statistically significant values ($P < 0.0188$) are shown in bold. Cognitive and education phenotypes are scored such that higher scores indicate better performance. The associations between the polygenic profile with the largest effect size (thresh) and each cognitive and education phenotype are presented. Thresh is the P -value threshold with the largest effect size.

(β between -0.01 and -0.02). Greater polygenic risk for large vessel disease stroke was associated with more errors in the memory task ($\beta = -0.01$). There was little change to the results for coronary artery disease when individuals diagnosed with cardiovascular disease were removed from the analyses, and little change for type 2 diabetes results when individuals with diabetes were removed (Table 3).

Cognitive–health pleiotropy: physical, physiological and anthropometric measures

There were significant genetic correlations between UK Biobank's educational attainment variable and body mass index (-0.23), and height (0.12), both obtained from the GIANT Consortium. There was a significant negative genetic correlation between body mass index and verbal-numerical reasoning (-0.12) and a significant positive genetic correlation with memory (0.15).

Greater polygenic risk for diastolic and systolic blood pressure (obtained from International Consortium for Blood Pressure), and body mass index were all associated with lower educational attainment (β of -0.02 , -0.04 and -0.09 , respectively). A polygenic profile for greater height was associated with higher educational attainment ($\beta = 0.07$). Higher verbal-numerical reasoning scores were associated with lower polygenic risk for body mass index ($\beta = -0.03$), and a polygenic profile for greater height ($\beta = 0.02$) and higher systolic blood pressure ($\beta = 0.01$). Results for systolic blood pressure changed little when individuals with hypertension were removed from the analysis (Table 3).

Multivariate models predicting cognitive variance using many polygenic profile scores

We next ran four multivariate regression models that included all 24 polygenic profile scores alongside the same covariates as were described above. This tested whether there was redundancy among the polygenic profile scores, and the extent to which including them all together in a multivariate model would improve the prediction of the cognitive phenotype. We compared the R^2 value of models including all the profile scores to models including only the covariates. The polygenic profile scores alone accounted for 3.33% of the variance in educational attainment of a college or university degree, 2.26% of the variance in verbal-numerical reasoning scores, 0.12% in reaction time and 0.16% in memory scores. See Supplementary Table 5 for full results.

DISCUSSION

The present study has combined the power of UK Biobank's very large genotyped and cognitively tested sample with the summary results of 24 large international GWAS consortia of physical and mental disorders and health-related traits. Two methods—LD score regression and polygenic profile scoring based on previous GWAS findings—discovered extensive cognitive–health pleiotropy and showed that it can be used to predict phenotypic variance between GWAS data sets. Our results provide comprehensive new findings on the overlaps between phenotypic cognitive ability levels, genetic bases for health-related characteristics such as height and blood pressure, and liabilities to physical and psychiatric disorders even in mostly healthy, non-diagnosed individuals. They make important steps toward understanding the specific patterns of overlap between biological influences on health and their consequences for key cognitive abilities. For example, some of the association between educational attainment—often used as a social background indicator—and health appears to have a genetic aetiology. These results should stimulate further research that will be informative about the specific genetic mechanisms of the associations found here, which likely involves both protective and detrimental effects of different genetic variants.

Findings for polygenic risk for coronary artery disease were not confounded by individuals with a diagnosis of cardiovascular disease, findings for type 2 diabetes were not confounded by individuals with a diagnosis of diabetes and findings for systolic blood pressure were not confounded by individuals with a diagnosis of hypertension. These results indicate that even in healthy individuals, being at high polygenic risk for coronary artery disease, type 2 diabetes or high blood pressure is associated with lower cognitive function and lower educational attainment.

Using LD score regression, we quantified for the genetic correlations from molecular genetic evidence between tests of cognitive ability and a wealth of health and anthropometric traits in over 100 000 individuals. As shown in Table 2, verbal-numerical reasoning and educational attainment showed a greater degree of pleiotropy than reaction time and memory, with many of the health and anthropometric variables studied here. Novel genetic correlations were quantified between cognitive function, using verbal-numerical reasoning, and schizophrenia, Alzheimer's disease and ischaemic stroke. It has not escaped our notice that there are multiple possible interpretations of these genetic correlations. Not only might particular genes contribute both to cognitive and health-related traits, but genetic variants relating to health conditions could have indirect effects on cognitive ability (for example, via medications used to treat disorders), and vice versa (for example, via cognitively associated lifestyle choices). See Solovieff *et al.*¹⁷ for discussion of these issues of causality and pleiotropy.

Perhaps counter-intuitively, our results indicated that the genetic variants associated with obtaining a college degree were also related to higher genetic risk of schizophrenia, bipolar disorder and autism, which for bipolar disorder and autism support the findings from a previous study.¹⁵ For the cognitive tests, only polygenic risk for autism was related with higher cognitive ability, in agreement with a previous study.²⁸ Genes related to bipolar disorder were negatively related to all of the cognitive tests, and genes related to schizophrenia even more so. Previous epidemiological studies indicate that both very high and very low educational achievement is associated with an increased risk of bipolar disorder²⁹ and high polygenic risk of schizophrenia and bipolar disorder were recently associated with higher levels of creativity.³⁰ The discrepancy between the cognitive and educational results may be explained by the age of the participants: if schizophrenia genes are detrimental to cognitive functioning only later in life, they may have differential effects on educational attainment, which tends to peak before age 30, and the cognitive tests, which were taken in UK Biobank at an average age of 56.9 years. It should also be noted the UK Biobank sample consists of individuals who are, on average, older than those in most schizophrenia genetic studies, have a higher level of education and are of a higher social class. It is also likely to have been the case that individuals in middle age with a history of serious mental illness will have been less likely than those without such a history to volunteer as UK Biobank participants. These demographic and clinical factors might have contributed to apparently contradictory findings with respect to cognitive function and previous educational attainment.

The educational attainment variable demonstrated pleiotropy with 20 of the 24 health-related variables, indicating that the genetic variants that collectively act to facilitate an individual's progress through the educational system to degree level make important contributions to many important health outcomes. One explanation for this is that the educational attainment variable shows the greatest degree of pleiotropy with general cognitive ability in childhood with a genetic correlation of 0.906. This could indicate that it is genes related to cognitive ability early in life that are responsible for the pleiotropy with health variables: educational attainment, therefore, might act as a proxy phenotype for general cognitive ability, as others have demonstrated.⁸

The significant genetic correlations across traits enabled the use of polygenic profile scores to predict phenotypic cognitive variance in the UK Biobank sample. The amount of variance explained by the polygenic profile scores for each UK Biobank cognitive phenotype is small, as would be expected by the fact that not all SNPs were genotyped, and those that were do not necessarily accurately tag the causal genetic variants. The multi-variate polygenic risk score analyses showed that additional variance can be accounted for when the polygenic liabilities of multiple disorders and traits are combined; this implies that there are risk alleles unique to each disorder and trait that affect cognitive and educational traits.

The results of the present study are supported by a previous study examining the genetic associations between polygenic profile scores for psychiatric and cognitive traits, and many phenotypic traits, showing comparable directions of effect.¹⁶ However, owing to the much smaller sample size (3000 versus 112 000 in the present study), the previous study yields insufficient power to detect several of the associations found in the present study. The same previous study also supported the results of the LD regression analyses of the present study between several psychiatric and cognitive traits, but the following traits show novel associations with cognitive ability and educational attainment in the present study: ischaemic stroke, infant head circumference and years of education.

The polygenic profile analysis replicated previous, smaller studies that showed associations between higher cognitive function and higher polygenic risk for autism²⁸ and lower polygenic risk for schizophrenia²¹ and stroke.²² We did not replicate the previous finding that higher cognitive function is associated with higher type 2 diabetes genetic risk,³¹ but we did find that higher type 2 diabetes genetic risk is associated with decreased likelihood of obtaining a college degree. Unlike a previous small, underpowered, study²³ we found that higher polygenic risk for Alzheimer's disease is associated with lower cognitive function.

To the extent that these genetic associations between cognitive and health measures are explained by shared genetic influences, they support the theoretical construct of bodily system integrity.³² System integrity was formulated as a latent trait which is manifest as individual differences in how effectively people meet cognitive and health challenges from the environment, and which has some genetic aetiology. Although it is recognized that some illnesses will cause changes in cognitive functions, system integrity suggests, in addition, that there is shared variance in how well different complex bodily systems operate and that this underlies correlations between higher cognitive functioning and good health and longevity.

The present study has a number of strengths. First, the large sample size of UK Biobank ($N > 100\,000$) affords powerful, robust tests of genetic association. Second, the participants took identical cognitive tests, which were always administered in the same computerized fashion, reducing any potential bias owing to heterogeneity in test content and administration. Third, all of the UK Biobank genetic data were processed in a consistent matter, on the same platform and at the same location. Fourth, our use of summary data from a large number of international GWAS studies allowed a comprehensive and detailed examination of shared genetic aetiology with cognitive ability across a wide range of health-related phenotypes, producing many of the first estimates of the genetic correlation between traits.

The present study has some limitations. The three cognitive tests were brief, bespoke measures. However, they covered three major cognitive domains (reasoning, processing speed and memory), showed acceptable internal consistency and had validity in that they showed the expected correlations with one another and with age and educational attainment.^{33,34} The verbal-numerical reasoning test has types of item that are the same as those found in tests of general cognitive ability. In addition,

verbal-numerical reasoning and educational attainment showed strong genetic correlations (0.812 and 0.906, respectively) with childhood general cognitive function. This suggests that the variance in these traits is largely the product of the same genetic variants that underpin general cognitive function. The GWAS studies we curated to perform LD score regression and extract the polygenic profile scores were often consortia studies, involving meta-analyses across data sets with substantial heterogeneity in sample size, genome-wide imputation quality and phenotypic measurement. We expect that, with larger and more consistent independent data sets, we would be able to use the polygenic profile scores to predict more variance in cognitive test performance. Some of the GWAS consortia studies did not have ethical approval to be used for genetic correlation and polygenic profile scoring analyses associated with education, meaning that we were unable to estimate a few correlations. Clustering in genetic population structure meant that we restricted the genotyped samples to individuals of white British ancestry. Our results thus need to be replicated in large samples of different genetic backgrounds; the sample sizes available in UK Biobank were not large enough for us to model, with adequate power, data from UK Biobank individuals of other ancestries.

The best method for showing pleiotropy using GWAS data would be to obtain the genome-wide significant hits from two GWAS and correlate the effect sizes. However, there are two reasons why this is suboptimal at present. The first reason is that many significant SNP hits are needed in multiple GWAS data sets, which is currently not possible. The second reason is that GCTA has shown that many true associations do not reach statistical significance owing to low power, therefore, SNPs that do not attain statistical significance should also be considered. Both LD regression and polygenic profile score analyses provide the opportunity to use the full GWAS output to examine pleiotropy.

Because the optimum number of SNPs used to generate a particular polygenic profile can differ between traits, we created five profile scores per physical and mental health trait and tested each in a regression against each of the UK Biobank cognitive traits to determine the score that explained the greatest variance in each cognitive trait. We found that these did differ between different trait combinations, suggesting that the amount of shared genetic aetiology differs between different pairs of traits. However, as pleiotropy was quantified using LD score regression to perform a single test for each pair of phenotypes, the multiple testing problems associated with the polygenic profile score method did not confound the estimates of pleiotropy shown here. Although the estimate of phenotypic variance explained by the polygenic profile method was small, this should be considered as the minimum estimate of the variance explained. Owing to pruning SNPs in LD, the PGRS method makes the assumption of a single causal variant being tagged in each LD block considered. If this assumption is not true for the phenotypes considered, the proportion of variance explained will be underestimated here.

CONCLUSION

It is notable that, a short while ago, a single result from several of the findings reported here would have been considered a major novel finding and reported as a study in itself.²⁰ With so many findings, it has not been possible fully to discuss their implications. For example, the genetic associations between infant head circumference and intracranial volume with educational attainment and verbal-numerical reasoning are important in themselves, as are many other cognitive-mental health and cognitive-physical health associations. Taken all together, these results provide a resource that advances the study of aetiology in cognitive epidemiology substantially.

CONFLICT OF INTEREST

IJD is a participant in UK Biobank. The remaining authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (<http://www.nature.com/mp>)

4.2.1. Conclusion

The results in Section 4.2 show, using two molecular genetic techniques—LDSR and PRS—that the association between cognitive ability and health is partly due to shared genetic influences. Whereas this Section did provide support for a shared genetic aetiology, the potential causality of the association was not investigated. The next Section of this Chapter will, therefore, assess whether cognitive ability causally affects physical health, or if physical health outcomes could be a risk factor for cognitive decline, using a bidirectional Mendelian randomization approach.

4.3. Cognitive ability and physical health: a Mendelian randomization study (accepted for publication in *Scientific Reports*)

Saskia P Hagenaars^{1,2,3}, Catharine R Gale^{1,2,4}, Ian J Deary^{1,2} and Sarah E Harris^{1,5}

1 Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK

2 Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK

3 Division of Psychiatry, University of Edinburgh, Edinburgh, EH10 5HF, UK

4 MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK.

5 Medical Genetics Section, University of Edinburgh Centre for Genomic and Experimental Medicine and MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK

Corresponding author: Sarah E Harris, Medical Genetics Section, University of Edinburgh Centre for Genomic and Experimental Medicine and MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK,
Email: sarah.harris@igmm.ed.ac.uk

Abstract

Causes of the association between cognitive ability and health remain unknown, but may reflect a shared genetic aetiology. This study examines the causal genetic associations between cognitive ability and physical health. We carried out two-sample Mendelian randomization analyses using the inverse-variance weighted method to test for causality between later life cognitive ability, educational attainment (as a proxy for cognitive ability in youth), BMI, height, systolic blood pressure, coronary artery disease, and type 2 diabetes using data from six independent GWAS consortia and the UK Biobank sample ($N = 112\,151$). BMI, systolic blood pressure, coronary artery disease and type 2 diabetes showed negative associations with cognitive ability; height was positively associated with cognitive ability. The analyses provided no evidence for casual associations from health to cognitive ability. In the other direction, higher educational attainment predicted lower BMI, systolic blood pressure, coronary artery disease, type 2 diabetes, and taller stature. The analyses indicated no causal association from educational attainment to physical health. The lack of evidence for causal associations between cognitive ability, educational attainment, and physical health could be explained by weak instrumental variables, poorly measured outcomes, or the small number of disease cases.

4.3.1. Introduction

Lower cognitive ability, lower educational attainment and greater cognitive decline are all associated with poorer health outcomes (Calvin et al., 2011; I. J. Deary et al., 2010; Wraw et al., 2015). Some of these associations possibly arise because of the effect of lower cognitive ability in childhood on later life health, others because illnesses may lower cognitive ability in later life. The causes of these associations are unclear, but some may reflect, in part, a shared genetic aetiology. Recent papers have reported genetic associations between cognitive ability and educational attainment, and a number of physical and mental health traits and diseases (Brendan K. Bulik-Sullivan et al., 2015a; Hagenaars et al., 2016b; Hill et al., 2016). These (Hagenaars et al., 2016b; Hill et al., 2016), and other papers (Banks & Mazzonna, 2012; Rietveld et al., 2014; Trampush et al., 2015), have shown successful use of educational attainment as a proxy for cognitive ability, showing phenotypic correlations between educational attainment and general cognitive ability around 0.50 (Banks & Mazzonna, 2012) and a genetic correlation of 0.72 (Hagenaars et al., 2016b).

Some of the reciprocal phenotypic associations between cognitive and physical health variables, and their genetic correlations, are as follows. Short stature has been consistently linked with lower cognitive ability (Keller et al., 2013; Silventoinen, Posthuma, Van Beijsterveldt, Bartels, & Boomsma, 2006). Molecular genetic studies have indicated positive genetic correlations between height and cognitive ability (Hagenaars et al., 2016b; Marioni et al., 2014a), as well as between height and educational attainment (Brendan K. Bulik-Sullivan et al., 2015a; Hagenaars et al., 2016b). Higher polygenic scores for height have been associated with better cognitive ability in adulthood (Hagenaars et al., 2016b). A causal association was reported between taller stature and educational attainment (not including individuals with a degree) in UK Biobank using a Mendelian randomization analysis (Tyrrell et al., 2016).

Multiple studies have shown associations between cognitive ability and cardiovascular risk factors. For example, lower childhood cognitive ability is associated with subsequent high blood pressure (Starr et al., 2004) and obesity (Belsky et al., 2013). However, higher BMI in mid-life (Dahl et al., 2010) and both hypertension and hypotension (Novak & Hajjar, 2010) are associated with lower cognitive ability and greater cognitive decline in later life. A negative genetic correlation has been identified between BMI, but not blood pressure, and educational attainment and cognitive ability in mid to late life (Brendan K. Bulik-Sullivan et al., 2015a; Hagenaars et al., 2016b) and a polygenic score for higher BMI is associated with lower cognitive ability in mid to late life and lower educational attainment (Hagenaars et al., 2016b), however, a polygenic score for higher systolic blood pressure is associated with lower educational attainment, but higher cognitive ability in mid to late life (Hagenaars et al., 2016b).

Similarly, associations have been identified between cognitive ability and cardio metabolic diseases. Childhood cognitive ability has been associated with developing diabetes (Möttus et al., 2013) and coronary artery disease (Lawlor, David Batty, Clark, McIntyre, & Leon, 2008) later in life. Diabetes (Rawlings et al., 2014) and coronary artery disease (Eggermont et al., 2012; Kovacic, Castellano, & Fuster, 2012) in midlife have been associated with greater cognitive decline later in life. A polygenic risk score for type 2 diabetes is associated with lower educational attainment, but not with cognitive ability in mid to late life (Hagenaars et al., 2016b), although one has been associated with reduced cognitive decline (Luciano et al., 2014). To date, no significant genetic correlation between diabetes and cognitive ability has been identified (Brendan K. Bulik-Sullivan et al., 2015a; Hagenaars et al., 2016b). A polygenic risk score for coronary artery disease is associated with lower educational attainment and lower mid to late life cognitive ability (Hagenaars et al., 2016b), and a negative genetic correlation was identified between coronary artery disease and educational attainment (Brendan K. Bulik-Sullivan et al., 2015a; Hagenaars et al., 2016b), but not cognitive ability in mid to late life (Hagenaars et al., 2016b).

The question arises as to whether the genetic cognitive-health associations caused by: 1) genes influencing health traits/diseases, and then those health traits/diseases subsequently influencing cognitive ability; 2) genes influencing cognitive ability, and then cognitive ability subsequently influencing health traits/diseases; 3) genes influencing general bodily system integrity(I. J. Deary, 2012) that influences both cognitive ability and health traits/diseases?

To try to make some progress in understanding causality of the correlation between cognitive ability and a number of physical and mental health traits, in the present report we used a bi-directional, two-sample Mendelian randomization (MR) approach (Bowden, Davey Smith, & Burgess, 2015). MR uses genetic variants as proxies for environmental exposures and is subject to the following assumptions: 1) the genetic variants are associated with the exposure; 2) the genetic variants are only associated with the outcome of interest via their effect on the exposure [i.e., there is no biological pleiotropy (the phenomenon whereby one SNP independently influences multiple traits), also called the exclusion restriction]; and 3) the genetic variants are independent of confounders. Figure 4-1 shows the Mendelian randomization study model; the instrumental variable, based on genome-wide significant SNPs from independent studies for the exposure, is used to estimate if the exposure (e.g. BMI) causally influences the outcome (e.g. cognitive ability).

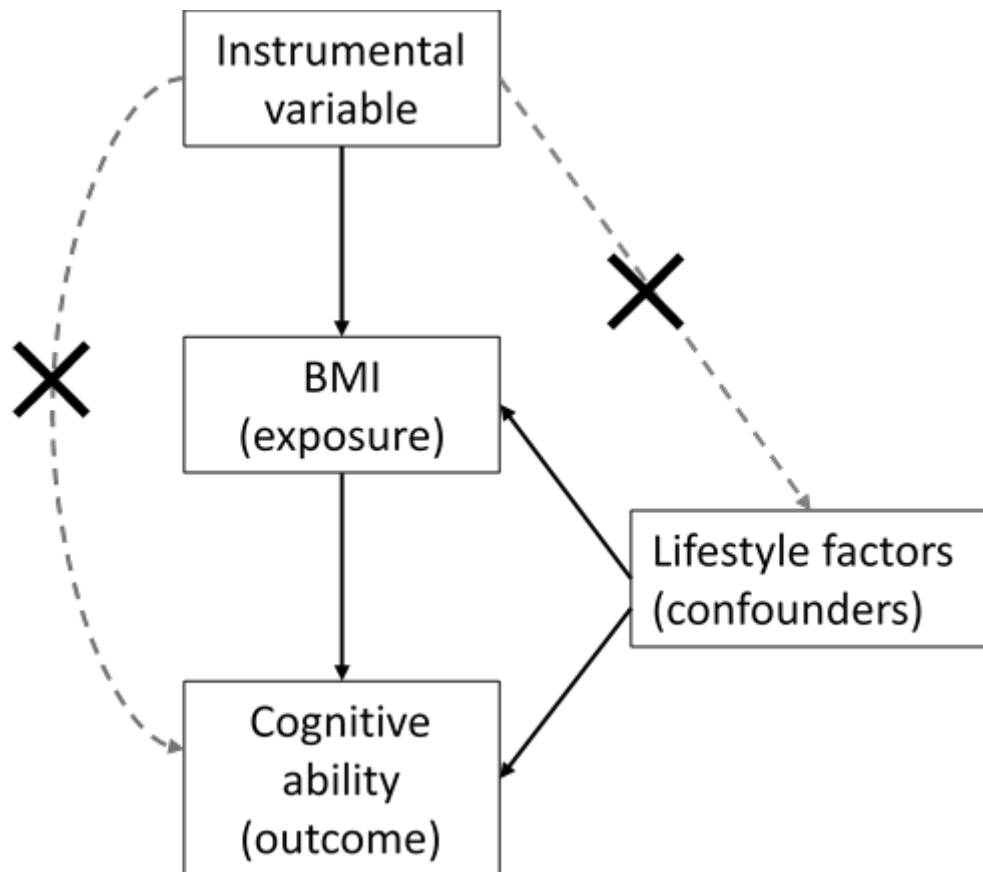


Figure 4-1. Model for Mendelian randomization study. The instrumental variable, based on genome-wide significant SNPs from independent studies for the exposure, is used to estimate if the exposure (e.g. BMI) causally influences the outcome (e.g. cognitive ability). The instrumental variable should be unrelated to potential confounders of the exposure-outcome association and should only affect the outcome via the exposure.

Individual single nucleotide polymorphisms (SNPs) are often found to be weak instruments for investigating causality because they often have small effect sizes. Using multiple SNPs can increase the strength of the instrument. However, this increases the chance of violating the MR assumptions, specifically violation of the assumption that the genetic variants affect the outcome only via the exposure. We used multiple genetic variants for a number of health-related traits and diseases, previously identified in genome-wide association studies, as instrumental variables to see if they predicted cognitive ability (verbal-numerical reasoning) in mid to later life in the UK Biobank. We then used genome-wide significant educational attainment SNPs as an instrumental variable to test whether genetic differences associated with

educational attainment (a proxy measure of cognitive ability in early life (Hill et al., 2016; Rietveld et al., 2014)) predicts later life health outcomes in the UK Biobank.

4.3.2. Methods

4.3.2.1. Sample

This study uses baseline data from the UK Biobank Study, a large resource for identifying determinants of human diseases in middle aged and older individuals (Sudlow et al., 2015). Around 500,000 community-dwelling participants aged between 37 and 73 years were recruited and underwent assessments between 2006 and 2010 in the United Kingdom. This included cognitive and physical assessments, providing blood, urine and saliva samples for future analysis, and giving detailed information about their backgrounds and lifestyles, and agreeing to have their health followed longitudinally. For the present study, genome-wide genotyping data were available on 112,151 individuals (58,914 females) aged 40–70 years (mean age=56.9 years, s.d.=7.9) after the quality control process which is described in more detail elsewhere (Hagenaars et al., 2016b). This study has been approved by the National Health Service (NHS) Research Ethics Service (approval letter dated 17th June 2011, reference: 11/NW/0382). This study has been completed under UK Biobank application 10279. All experiments were performed in accordance with guidelines and regulations from these committees. Written informed consent was obtained from each subject.

4.3.2.2. Measures

Body mass index

Body mass index (BMI) was calculated as $\text{weight(kg)}/\text{height(m)}^2$, and measured using an impedance measure, i.e. a Tanita BC418MA body composition analyser, to estimate body composition. We used the average of the two methods when both measures were available ($r = 0.99$); if only one measure was available, that measure was used ($N = 1629$). 291 individuals

did not have information on BMI. One outlier was excluded based on visual inspection of the BMI distribution ($\text{BMI} > 50$). 111,712 individuals had valid BMI and genetic data.

Height

Standing and sitting height (cm) were measured using a Seca 202 device. We used standing height and excluded one individual based on the visual inspection of the height distribution with a standing height < 125 cm and a sitting/standing height ratio < 0.75 . 111,959 had valid height and genetic data.

Systolic blood pressure

Systolic blood pressure was measured twice, a few moments apart, using the Omron Digital blood pressure monitor. A manual sphygmomanometer was used if the digital blood pressure monitor could not be employed ($N = 6652$). Systolic blood pressure was calculated as the average of measures at the two time points (for either automated or manual readings). Individuals with a history of coronary artery disease were excluded from the analysis ($N = 2513$). Following the recommendation by Tobin, Sheehan, Scurrah, and Burton (2005), 15 mmHg was added to the average systolic blood pressure of individuals taking antihypertensive medication ($N = 10,988$). Individuals with a systolic blood pressure (after correcting for medication) more than 4 SD from the mean were excluded from future analyses ($N = 75$). After all exclusions, 106,759 individuals remained with valid blood pressure and genetic data.

Coronary artery disease

UK Biobank participants completed a touch screen questionnaire on past and current health, which included the question “Has a doctor ever told you that you have had any of the following conditions? heart attack/angina/stroke/high blood pressure/none of the above/prefer not to answer”. This was followed by a verbal interview with a trained nurse who was made aware if the participant had a history of certain illnesses and confirmed these diagnoses with the

participant. For the present study, coronary artery disease was defined as a diagnosis of myocardial infarct or angina, reported during both the touchscreen and the verbal interview in individuals with genetic data (N = 5288). The control group (N = 104,784) consisted of participants who reported none of the following diseases (based on the non-cancer illness code provided by UK Biobank): myocardial infarction, angina, heart failure, cerebrovascular disease, stroke, transient ischaemic attack, subdural haemorrhage, cerebral aneurysm, peripheral vascular disease, leg claudication/intermittent claudication, arterial embolism.

Type 2 diabetes

Type 2 diabetes case-control status was created using the same method as described by Wood et al. (2014), for all individuals with genetic data based on the interim release of UK Biobank. Cases included participants who reported type 2 diabetes or generic diabetes during the nurse interview, started insulin treatment at least one year after diagnosis, were older than 35 years at the time of diagnosis, and did not receive a diagnosis one year prior to baseline testing (N = 3764). The control group consisted of participants who did not fulfil these criteria, and did not report a diagnosis of type 1 diabetes, diabetes insipidus and gestational diabetes (N = 108,015).

Years of education

As part of the sociodemographic questionnaire in the study, participants were asked, “Which of the following qualifications do you have? (You can select more than one)”. Possible answers were: “College or University Degree/A levels or AS levels or equivalent/O levels or GCSE or equivalent/CSEs or equivalent/NVQ or HND or HNC or equivalent/Other professional qualifications e.g. nursing, teaching/None of the above/Prefer not to answer”. For the present study, a new continuous variable was created measuring ‘years of education completed’. This was based on the ISCED coding, using the 1997 International Standard Classification of Education (ISCED) of the United Nations Educational, Scientific and Cultural Organization (UNESCO, 2006). See the Table 4-1 for further details. Individuals who

reported that they had a NVQ or HND or HNC degree, individuals who reported other qualifications, and individuals who preferred not to answer were excluded from analyses. The reason for these exclusions was as follows: the first two categories would correspond to 15 and 19 years of education according to the ISCED coding; regarding their mean scores on cognitive ability tests, this might not be the right place for these two degree levels in the ordered hierarchy of educational attainments (Supplementary Figure 1). For the current study, years of education was used a proxy phenotype for cognitive ability (Hagenaars et al., 2016b; Hill et al., 2016; Rietveld et al., 2014). A total of 97,550 individuals had valid data for the years of education variable.

Table 4-1. Coding for years of education in UK Biobank based on the ISCED coding. ISCED, 1997 International Standard Classification of Education of the United Nations Educational, Scientific and Cultural Organization.

UK Biobank degree level	UK Biobank code	ISCED code	Years of education (based in ISCED code)	N
College or university degree	1	5	20 (19 +1)	33,852
A levels/AS levels or equivalent	2	3	13	12,560
O levels/GCSEs or equivalent	3	2	10	24,802
CSEs or equivalent	4	2	10	6064
NVQ or HND or HNC or equivalent	5	NA	NA	7788
Other professional qualification eg: nursing, teaching	6	NA	NA	5776
None of the above	-7	1	7	20,272
Prefer not to answer	-3	NA	NA	953

Cognitive ability

Cognitive ability was measured using a 13-item touchscreen computerized verbal-numerical reasoning test. The test included six verbal and seven numerical questions, all with multiple-choice answers, with a two-minute time limit. An example verbal item is: ‘If some flinks are plinks and some plinks are stinks then some flinks are definitely stinks?’ (possible answers: ‘True/False/Neither-true-nor-false/do not know/prefer not to answer’). An example numerical item is: ‘If sixty is more than half of seventy-five, multiply twenty-three by three. If not subtract 15 from eighty-five. Is the answer?’ (possible answers: ‘68/69/70/71/72/do not know/prefer not to answer’). The cognitive ability score was the total score out of 13 (further detail can be found in Hagenaars et al. (2016b)). This test was introduced at a later stage during baseline assessment and only a subset of individuals therefore completed this test. A total of 36,035 had valid cognitive ability and genetic data.

4.3.2.3. Covariates

All analyses were adjusted for the following covariates: age when attending assessment centre, sex, genetic batch and array, and the first ten genetic principal components for population stratification.

4.3.2.4. Instrumental variables

SNPs used in the instrumental variables were extracted from the imputed UK Biobank genotypes interim release including 112,151 individuals after quality control. Details on the quality control process have been published previously (Hagenaars et al., 2016b). All instrumental variables were created based on SNPs that reached genome-wide significance in the largest available GWAS in European samples for the variables of interest (BMI (Locke et al., 2015), height (Wood et al., 2014), systolic blood pressure (The International Consortium for Blood Pressure Genome-Wide Association Studies, 2011), coronary artery disease (Schunkert et al., 2011), type 2 diabetes (Morris et al., 2012) and educational attainment

(Okbay et al., 2016b)). For educational attainment, we downloaded the summary statistics based on the discovery GWAS only, which did not include the UK Biobank sample. Corresponding SNPs used in the instrumental variables were then extracted from the imputed UK Biobank's interim release of genotypes, which amounted to 112,151 individuals of self-reported White British ancestry after quality control. Details on the quality control process have been published previously (Hagenaars et al., 2016b). SNPs out of Hardy-Weinberg equilibrium (HWE, $p < 1 \times 10^{-6}$), with an imputation quality below 0.9, or individual genotypes with a genotype probability below 0.9 and strand ambiguous SNPs were excluded from the instrumental variables. The individual variants were recoded as 0, 1 or 2 according to the number of trait increasing alleles. Table 4-2 includes information on the number of SNPs included, the reference paper, and the amount of variance explained by the instrumental variables for the corresponding variable of interest. Supplementary Table 3a-f provides details of the included SNPs.

Table 4-2. Information about instrumental variables.

Phenotype	SNPs included	total SNPs N	Reference	Unavailable in HWE UK Biobank	p < 10 ⁻⁶	p < imputation < 0.9	AT/CG SNPs
BMI	70	76	236,231	Locke et al. Nature 2015; 518: 197-206. PMID: 25673413	1	3	2
Height	331	405	253,288	Wood et al. Nat Genet 2014; 11: 1173-86. PMID: 25282103	3	5	64
Systolic blood pressure	20	25	69,395	Ehret et al. Nature 2011; 478: 103-109. PMID: 21909115	0	0	5
Coronary artery disease	19	23	22,233 cases; Schunkert et al. Nat Genet 2011; 64,762 controls 43: 333-338. PMID: 21378990	0	0	0	4
Type 2 diabetes	9	9	12,171 cases; Morris et al. Nat Genet 2012; 44: 56,862 controls 981-990. PMID: 22885922	0	0	0	0
Educational attainment	63	74	293,723	Okbay et al. Nature 2016; 533: 539-542. PMID: 27225129 http://ssgac.org/documents/EduYe_ars_Discovery_5000.txt	2	4	5

4.3.2.5. Statistical analysis

Phenotypic associations

We performed linear regression analysis using BMI, height, systolic blood pressure, coronary artery disease, and type 2 diabetes to predict cognitive ability. We regressed BMI, height, and systolic blood pressure against educational attainment in a linear regression model; coronary artery disease and type 2 diabetes were regressed against educational attainment in logistic regression models.

Mendelian randomization analysis

The Mendelian randomization analysis was performed using inverse variance weighted regression analysis based on SNP level data, with each instrumental variable (IV) consisting of multiple SNPs (Bowden et al., 2015). The inverse variance weighted method is based on a regression of two vectors with the intercept constrained to zero; the genetic variant with the exposure association, and the genetic variant with the outcome association (Figure 4-1). By constraining the intercept to zero, this method assumes that all variants are valid instrumental variables. We performed an association analysis between each SNP in the instrumental variable for the exposure and the exposure itself (IV - exposure), as well as between the instrumental variable for the exposure and the outcome (IV - outcome). We then used the vector of the instrumental variable-outcome association analyses against the vector of the instrumental variable-exposure analyses. This association (vector IV - outcome ~ vector IV - exposure) was weighted by the standard error of the original IV-outcome association, to correct for minor allele frequency, as described by Bowden et al. (2015). Power calculations for the MR analyses can be found in Supplementary Table 1. No sensitivity analyses were performed due to the lack of significant causal associations.

4.3.3. Results

4.3.3.1. Health outcomes predicting cognitive ability

BMI, height, systolic blood pressure, and coronary artery disease predicted performance on the verbal-numerical reasoning test of cognitive ability (Table 4-3). A 1 SD higher BMI was associated with a 0.05 SD lower score for cognitive ability [$\beta = -0.05$, 95% CI = $-0.06 - (-0.04)$]. A 1 SD greater height was associated with a 0.18 SD higher score for cognitive ability [$\beta = 0.18$, 95% CI = $0.17 - 0.20$]. A 1 SD higher systolic blood pressure was associated with a 0.05 SD lower score for cognitive ability [$\beta = -0.05$, 95% CI = $-0.06 - (-0.04)$]. Individuals with coronary artery disease had, on average, a 0.27 SD lower score for cognitive ability [$\beta = -0.27$, 95% CI = $-0.32 - (-0.21)$]. Individuals with type 2 diabetes had, on average, a 0.06 SD lower score for cognitive ability [$\beta = -0.06$, 95% CI = $-0.12 - 0.01$]. The Mendelian randomization inverse variance weighted analyses, with the five health outcomes as the exposures, and cognitive ability as the outcome, did not provide any causal evidence for any of these associations.

Table 4-3. Phenotypic and genetic associations, using Mendelian randomization analysis, between five health instrumental variables and cognitive ability, using the verbal-numerical reasoning test. Significant associations are in bold. OR, odds ratio; MR-IVW, Mendelian randomization - inverse variance weighted method.

Cognitive ability SNPs (nr)	Phenotypic: health outcomes – cognitive ability			MR-IVW: health SNPs – cognitive ability		
	Beta	95% CI	p	Beta	95% CI	p
BMI (70)	-0.049	-0.059 – (-0.039)	1.51×10⁻²⁰	-0.035	-0.147 – 0.077	0.5439
Height (331)	0.1816	0.166 - 0.197	5.53×10⁻¹²⁴	0.026	-0.009 – 0.061	0.1329
Systolic blood pressure (20)	-0.0492	-0.061 – (-0.037)	2.24×10⁻¹⁷	-0.002	-0.010 – 0.006	0.6355
Coronary artery disease (19)	-0.2651	-0.316 – (-0.214)	4.62×10⁻²⁵	-0.018	-0.045 – 0.009	0.2343
Type 2 diabetes (9)	-0.0634	-0.120 – (-0.007)	0.0292	0.010	-0.019 – 0.039	0.5316

4.3.3.2. Education predicting health outcomes

Educational attainment, as measured by years of education, predicted BMI, height, systolic blood pressure, type 2 diabetes and coronary artery disease (Table 4, Figure 2). The difference between 7 and 20 years of education was associated with a 0.37 SD lower BMI [$\beta = -0.37$, 95% CI = -0.39 – (-0.35)], 0.31 SD taller stature [$\beta = 0.31$, 95% CI = 0.30 – 0.32], 0.20 lower SBP [$\beta = -0.20$, 95% CI = -0.22 – (-0.19)], 0.58 lower odds of type 2 diabetes [OR = 0.58, 95% CI = 0.52 – 0.64], and 0.40 lower odds of coronary artery disease [OR = 0.40, 95% CI 0.37 – 0.43]. The differences between the other groups (7 versus 10 and 13 years of education) can be found in Supplementary Table 2. In every case, the Mendelian randomization inverse variance weighted method did not show a causal effect of educational attainment on the health outcomes. The full results can be found in Table 4-4.

Table 4-4. Phenotypic and genetic associations, using Mendelian randomization analysis, between the educational attainment instrumental variable and five health outcomes. Significant associations are in bold. OR, odds ratio; MR-IVW, Mendelian randomization - inverse variance weighted method.

	Educational attainment		health		Educational attainment SNPs – health outcomes (63 SNPs)	
	Beta	95% CI	p	Beta	95% CI	p
Phenotypic (7 vs 20 years of education)						
	Beta	95% CI	p	Beta	95% CI	p
BMI	-0.367	-0.385 – (-0.349)	<1.00×10⁻¹³⁰	-0.026	-0.157 – 0.105	0.6986
Height	0.312	0.300 – 0.324	<1.00×10⁻¹³⁰	0.021	-0.106 – 0.148	0.7479
Systolic blood pressure	-0.204	-0.222 – (-0.187)	5.61×10⁻¹¹⁸	-0.003	-0.097 – 0.091	0.9493
Type 2 diabetes	OR: 0.575	0.522 – 0.635	2.41×10⁻²⁸	0.022	-0.703 – 0.747	0.5642
Coronary artery disease	OR: 0.397	0.365 – 0.432	3.73×10⁻¹⁰¹	0.015	-0.047 – 0.077	0.6440

4.3.4. Discussion

This study was designed to investigate causes of the well replicated finding that lower cognitive ability is associated with poorer health outcomes (Calvin et al., 2011; I. J. Deary et al., 2010; Wraw et al., 2015). It used a bidirectional two-sample MR approach to investigate this. We found no evidence for causal association between several health outcomes and cognitive ability, in middle and older age, or between educational attainment and physical health.

Tyrrell et al. (2016) showed a significant causal association between taller stature and time spent in full time education in UK Biobank. They did not find a causal association between taller stature and degree level. The measure of time spent in full time education in UK Biobank excluded individuals who reported having a college degree, which could explain the discrepancy in results. The current study did include individuals who reported having a college degree, however used a categorical measure of four categories, whereas (Tyrrell et al., 2016) used a continuous measure of time spent in full time education. In a non-peer-reviewed (at the time of writing) study, Tillmann et al. (2017) did report a causal association from educational attainment to coronary artery disease and BMI using a two-sample MR approach based on two independent consortia. They used data from two independent GWAS consortia, including 349,306 individuals for educational attainment, 194,427 (63,746 cases) individuals for coronary artery disease, and 339,224 individuals for BMI. The current study used the same data for educational attainment on a subset of individuals ($N = 293,723$), and 111,712 individuals with BMI data; however, coronary artery disease was based on self-report diagnosis in UK Biobank, which included 110,072 (5288 cases) individuals. The summary level data for coronary artery disease in the Tillmann et al. (2017) report included both European and East-Asian individuals, whereas the current study only includes individuals of White British ancestry. They (Tillmann et al., 2017) excluded overlapping cohorts between

educational attainment and coronary artery disease data; however, it is unclear if overlapping cohorts were excluded for BMI.

Another explanation for the lack of causal associations in the present study could be the high polygenic aetiology of the traits analysed in this study. Instrumental variables for cardiovascular disease, type 2 diabetes, blood pressure, and educational attainment explain a small amount of the variance in the exposure. A better instrumental variable would be expected to explain a substantial amount of the variance of the exposure. As shown by the power calculations (Supplementary Table 1), all instrumental variables (except BMI and systolic blood pressure) had sufficient power to detect the same magnitude of association as the observational estimates. The low power for BMI and systolic blood pressure potentially explains the lack of association with cognitive ability. A previous study by the current authors indicated a degree of genetic overlap between cognitive ability and health across the genome (Hagenaars et al., 2016b). The idea of pleiotropy between health and cognitive ability is consistent with the theoretical construct of bodily system integrity (I. J. Deary, 2012), whereby a latent trait is manifest as individual differences in how effectively people meet cognitive and health challenges from the environment, and which has some genetic aetiology.

Strengths of this study include the large sample size of UK Biobank, the participants of which all took the same cognitive tests, completed the same questionnaires and answered the same interview questions, in contrast to most genetic studies, where assessments across different cohorts often vary. A further strength is the fact that all of the UK Biobank genetic data were processed in a consistent matter, on the same platform and at the same location. The genetic variants on which the instrumental variables originated used the largest available GWAS at moment of testing.

Limitations of this study include the fact that cognitive ability was only measured on a subset of the UK Biobank participants and that it was a bespoke test. A second major limitation was that there is no published large genome-wide association study of cognitive ability in early life from which we could obtain genetic variants to use as an instrumental variable. Therefore, we used genome-wide significant SNPs associated with educational attainment as our early life cognitive ability instrument. A further limitation is the case-control ascertainment in UK Biobank, as the current study based case-control status on self-report measures. This may have led to misclassification of disease status, causing a likely bias towards the null hypothesis (L. Zheng et al., 2012).

Overall, this study found phenotypic cognitive-physical health associations, but did not find evidence for causal associations between cognitive ability and physical health. This may be due to weak instrumental variables, poorly measured outcomes, or the small numbers of disease cases. Future work should therefore focus on stronger instrumental variables, as well as better measurement of the outcome variables.

4.3.5. Acknowledgements

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4.3.6. Author contributions

All authors contributed to the design of the study. UK Biobank collected all data and was involved in pre-processing the genetic data. SPH extracted, pre-processed, and analysed the

data. SPH and SEH wrote the main manuscript text. All authors discussed and commented on the manuscript.

4.3.7. Competing financial interests

The authors declare no competing financial interests.

4.4. Conclusion

As discussed by Hagenaars et al. (2016b) in Section 4.2, the finding that the association between different measures of cognitive ability and health is partly due to shared genetic influences, represents a first step in advancing the understanding of the mechanisms that underlie the association between cognitive ability and health. A further step has been made to untangle the potential causal pathways between cognitive ability and health in Section 4.3; however, no evidence of such pathways was found. Identifying bidirectional causal processes between cognitive ability and health, remains a challenge for future work to address. A recent study did show a causal association between educational attainment and coronary artery disease using a Mendelian randomization approach, this will be discussed in more detail in Section 8.1.1. The next Chapter will examine the genetic architecture of an executive function measure in order to better understand the shared genetic aetiology with other cognitive abilities.

5. Genetic contributions to trail making test performance in UK Biobank

5.1. Introduction

The two studies in Chapter 4 examined the genetic association between different measures of cognitive ability and health, and the potential causal pathways between those measures of cognitive ability and physical health. The verbal-numerical reasoning, reaction time, and memory tests in UK Biobank are non-standardized bespoke measures of cognitive ability. It is therefore more difficult to generalize findings across other measures of cognitive ability. UK Biobank introduced follow-up tests, which included a web-based assessment of cognitive ability. The Trail Making Test was part of this web-based assessment, and is a widely used, standardized measure of executive function. Phenotypic studies have indicated that both fluid cognitive ability and processing speed are involved in the Trail Making Test (Salthouse, 2011a, 2011b). This Chapter will therefore explore the genetic architecture of the Trail making test and the potential shared genetic aetiology with other cognitive abilities, both within UK Biobank and in independent samples. This paper has been submitted for publication at *Molecular Psychiatry* and is included in full in Section 5.2.

5.2. Genetic contributions to trial making test performance in UK Biobank (submitted).

Saskia P Hagenaars^{1,2,3}, Simon R Cox^{1,2}, W David Hill^{1,2}, Gail Davies^{1,2}, David CM Liewald^{1,2},
CHARGE consortium Cognitive Working Group, Sarah E Harris^{1,4}, Andrew M McIntosh^{1,3},
Catharine R Gale^{1,2,5*}, Ian J Deary^{1,2*#}

¹ Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK

² Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK

³ Division of Psychiatry, University of Edinburgh, Edinburgh, EH10 5HF, UK

⁴ Medical Genetics Section, University of Edinburgh Centre for Genomic and Experimental Medicine and MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK

⁵ MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, SO16 6YD, UK

*These authors contributed equally to the work.

Corresponding author,

Ian J. Deary

Centre for Cognitive Ageing and Cognitive Epidemiology

Department of Psychology

University of Edinburgh

7 George Square

Edinburgh, EH8 9JZ

Scotland, UK

Telephone: +44 131 650 3452

Fax: +44 131 651 1771

ian.deary@ed.ac.uk

Abstract

The Trail Making Test is a widely used test of executive function and has been thought to be strongly associated with general cognitive function. We examined the genetic architecture of the trail making test and its shared genetic aetiology with other tests of cognitive function in 23 821 participants from UK Biobank. The SNP-based heritability estimates for trail-making measures were 7.9 % (part A), 22.4 % (part B), and 17.6 % (part B – part A). Significant genetic correlations were identified between trail-making measures and verbal-numerical reasoning ($r_g > 0.6$), general cognitive function ($r_g > 0.6$), processing speed ($r_g > 0.7$), and memory ($r_g > 0.3$). Polygenic profile analysis indicated considerable shared genetic aetiology between trail making, general cognitive function, processing speed, and memory (standardized β between 0.03 and 0.08). These results suggest that trail making is both phenotypically and genetically strongly associated with general cognitive function and processing speed.

5.2.1. Introduction

The Trail Making Test (TMT) is widely used in both research and clinical settings as a test of some aspects of executive function (Delis, Kaplan, & Kramer, 2001; Lezak, Howieson, & Loring, 2004; Reitan & Wolfson, 1985). The TMT is usually given as two parts, from which three measures are derived. In Part A (TMT-A), participants are required to connect an array of numbers in ascending order, by drawing a continuous line (trail) between them as quickly and accurately as possible. Part B (TMT-B) requires participants to connect an array of both numbers and letters in *alternating* ascending order (1, A, 2, B, 3, C, etc.) with the same emphasis on speed and accuracy (Supplementary Figure 1). Subtracting TMT-A completion time from that of TMT-B (TMT B minus A) is thought to allow the relative contributions of visual search and psychomotor speed to be parsed from the more complex executive functions (such as cognitive flexibility) required to alternate between numbers and letters (Arbuthnott & Frank, 2000; Bowie & Harvey, 2006; Gläscher et al., 2012; Kortte, Horner, & Windham, 2002; Strauss, Sherman, & Spreen, 2006).

TMT performance has been ascribed to a number of cognitive processes, “including attention, visual search and scanning, sequencing and shifting, psychomotor speed, abstraction, flexibility, ability to execute and modify a plan of action, and ability to maintain two trains of thought simultaneously” (Salthouse, 2011b, p. 222). It is considered a useful tool in research and clinical practice due to the sensitivity of the task (particularly TMT B and B-A) to frontal lobe damage (in some, but not other studies; see MacPherson, Della Sala, Cox, Girardi, and Iveson (2015)) and dementia (Amieva et al., 1998; Ferman et al., 2006; Rasmusson, Zonderman, Kawas, & Resnick, 1998). There are declines in both TMT A and B performance in ageing (Giovagnoli et al., 1996; Hamdan & Hamdan, 2009; Hashimoto et al., 2006; Hester, Kinsella, Ong, & McGregor, 2005; MacPherson et al., 2015; Periañez et al., 2007; Salthouse,

2011a; Seo et al., 2006). There is also evidence for performance deficits on TMT B in mood disorders (Marvel & Paradiso, 2004), and in patients with schizophrenia and their relatives (Aleman, Hijman, Haan, & Kahn, 1999; Gilvarry, Russell, Hemsley, & Murray, 2000; Heinrichs & Zakzanis, 1998; Periañez et al., 2007; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Wölwer & Gaebel, 2002; Zalla et al., 2004)

Family-based and twin-based studies have provided evidence for a genetic contribution to individual differences in trail making, estimating the heritability for trail making part A between 0.23 and 0.38, and between 0.39 and 0.65 for trail making part B (Buyske et al., 2005; Knowles et al., 2014; Vasilopoulos et al., 2012). A recent genome-wide association study (GWAS) of trail making part A and part B in a sample of around 6000 individuals did not find any genome-wide significant hits (Ibrahim-Verbaas et al., 2016); however, GWAS of other cognitive phenotypes have demonstrated that much larger sample sizes are required to reliably identify significant genetic loci (G. Davies et al., 2015a; G. Davies et al., 2016b). Trail making is thought to have genetic influences that are shared with other cognitive abilities, with a twin-based genetic correlation of 0.48 reported between trail making, measured as the ratio between trail making part A and trail making part B, and general cognitive function, and 0.52 with working memory (T. Lee et al., 2012).

In addition to a relatively poor understanding of the molecular genetic underpinnings of TMT, its cognitive and psychometric architecture merits further research. Specifically, it is unclear whether the cognitive abilities required for TMT-B performance are distinct from other cognitive domains, because TMT A and B scores correlate with measures of general cognitive function and processing speed (correlation coefficient estimates range from ~0.3 to ~0.7; (Salthouse, 2011a, 2011b)) (Corrigan & Hinkeldey, 1987; Goul & Brown, 1970; Steinberg, Bieliauskas, Smith, & Ivnik, 2005; Vasilopoulos et al., 2012; Waldmann, Dickson, Monahan, & Kazelskis, 1992). Evidence from cognitive-ageing studies further suggests a strong overlap

between TMT performance and other cognitive domains, because age-related decline in processing speed and working memory account for much of the age effects on TMT-B (Oosterman et al., 2010; Salthouse, 2011a, 2011b; Sanchez-Cubillo, Perianez, Adrover-Roig, & Rodriguez-Sanchez, 2009). However, reliably identifying the cognitive processes that underpin cognitive test performance using phenotypic correlational analyses alone is sub-optimal, (e.g. Cox et al., 2014; Delis, Jacobson, Bondi, Hamilton, & Salmon, 2003; Rabbitt, 2011). Rather, the interpretation of relationships between TMT performance and other cognitive abilities such as general cognitive function, may be enhanced by considering and comparing their respective shared and unshared causes, including their genetic architecture. By examining the shared genetic architecture of TMT and other measures of cognitive ability, the current study will aid a better understanding of potential biological pathways involved in cognitive ability.

The aim of the present study is to: 1) add to the understanding of the genetic architecture of trail making; and 2) to explore the overlap between genetic architecture of TMT performance and other cognitive abilities, including general cognitive function. Although several studies have examined the genetic architecture of the trail making test and its overlap with other cognitive abilities, they had relatively low power. The largest TMT GWAS (N ~ 6000) to date used a variety of assessments across multiple cohorts across multiple countries, potentially leading to heterogeneity in both sample composition and in the cognitive measures (Ibrahim-Verbaas et al., 2016). The current study design, using >23,000 UK Biobank participants, mitigates such confounds: the almost four-fold increase in sample size yields greater statistical power, and the single sample reduces heterogeneity in genetic testing and in phenotype, because all participants had white British ancestry and took the same TMT test with the same instructions. In addition, we add to this significantly larger GWAS than has previously been conducted with: (1) estimates of the SNP-based heritability of TMT performance, and (2) an examination of genetic overlap among the different TMT test measures and with other

cognitive functions, using polygenic profile analysis and genetic correlations in independent samples.

5.2.2. Materials and methods

5.2.2.1. Participants

UK Biobank is a large resource which aims to identify determinants of human diseases in middle aged and older individuals (<http://www.ukbiobank.ac.uk>) (Sudlow et al., 2015). A total of 502,655 community-dwelling individuals aged between 37 and 73 years were recruited in the United Kingdom between 2006 and 2010. Baseline assessment included cognitive testing, personality self-report, and physical and mental health measures. For the present study, genome-wide genotyping data were available for 112,151 participants (58,914 females, 53,237 males) after quality control (see below). They had a mean (SD) age of 56.9 (7.9) years (range 40 to 73 years). UK Biobank received ethical approval from the Research Ethics Committee (REC reference for UK Biobank is 11/NW/0382). This study was completed under UK Biobank application 10279. Figure 5-1 shows the study flow for the present study.

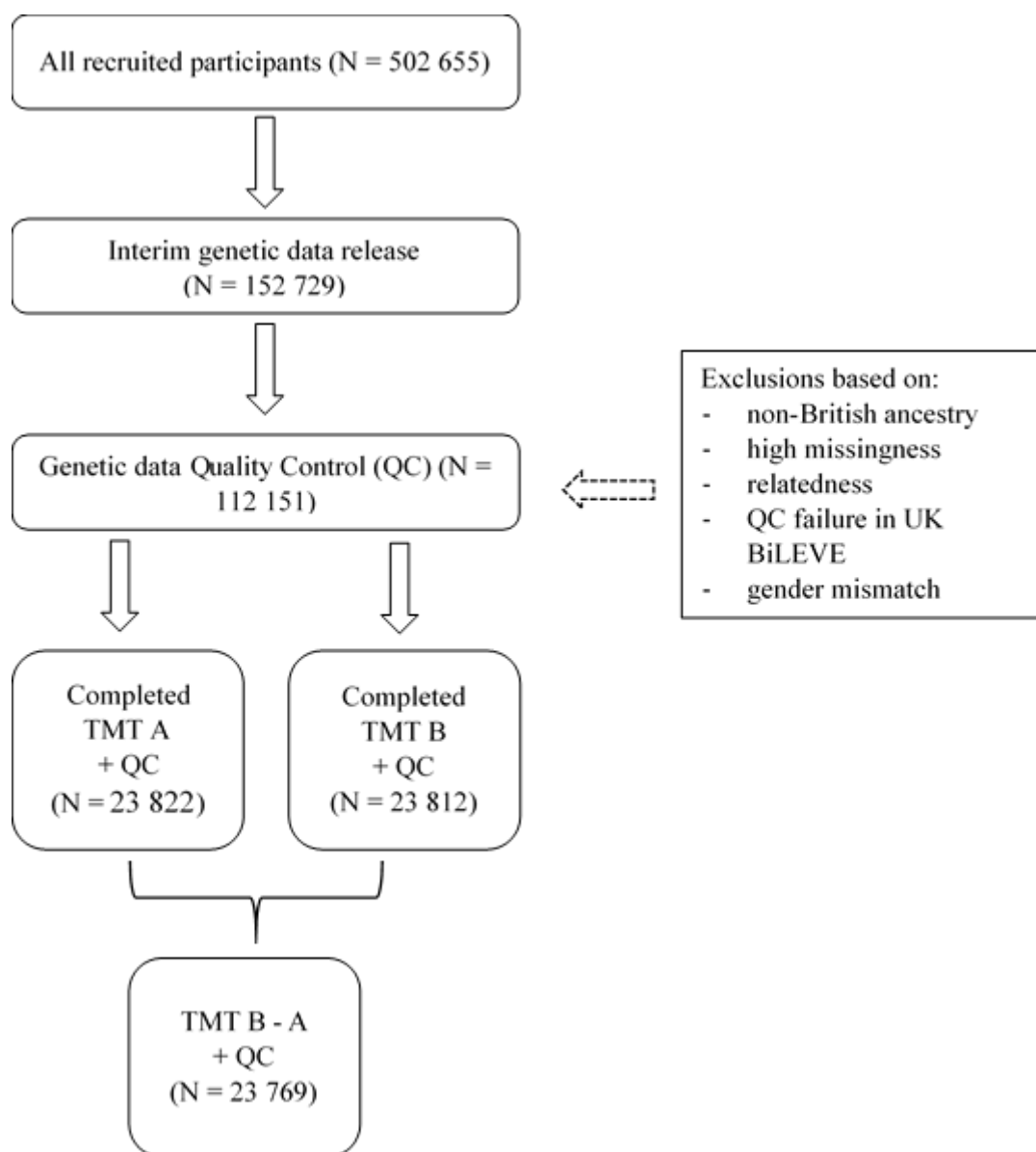


Figure 5-1. Flow diagram of participant selection.

5.2.2.2. Measures

The trail making test parts A (TMT A) and B (TMT B) were introduced at a follow up testing wave in UK Biobank, between 2014 and 2015. For TMT A, participants were instructed to connect numbers (1 – 25) consecutively (which were quasi-randomly distributed on the touchscreen) as quickly as possible in ascending order by selecting the next number. TMT B is similar, but letters (A – L) and numbers (1 – 13) had to be selected in alternating ascending order, e.g. 1 A 2 B 3 C etc. The intervals between touching two points was timed in seconds

using a Javascript timer. The total time (in seconds) to complete the trail making test (part A or B) was derived by summing the interval values between two points. Nine out of 23,821 individuals who scored >250 seconds for TMT B were excluded. Owing to positively skewed distributions, both TMT A and TMT B scores were log-transformed prior to further analyses. The difference between the raw scores for TMT A and TMT B was computed as TMT B minus TMT A (TMT B-A). 52 out of 23,821 individuals with scores <-50 or >150 were removed from TMT B-A. After exclusions, 23,822 individuals with genetic data completed TMT A, 23,812 individuals with genetic data completed TMT B, and 23,769 individuals had complete information for TMT B-A. The three trail making measures have been scored such that a higher score indicates better performance. This study also used the verbal-numerical reasoning test from UK Biobank (VNR, N = 36,035), which consisted of a 13-item questionnaire assessing verbal and arithmetical deduction (Chronbach α reliability = 0.62) as described by Hagenaars et al. (2016b).

5.2.2.3. Genotyping and quality control

The interim release of UK Biobank included genotype data for 152,729 individuals, of whom 49,979 were genotyped using the UK BiLEVE array and 102,750 using the UK Biobank axiom array. These arrays have over 95% content in common. Details of the array design, genotyping procedures and quality control details have been published elsewhere (Hagenaars et al., 2016b; Wain et al., 2015). UK Biobank released an imputed dataset as part of the interim data release. More details can be found at the following URL: <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020>. A minor allele frequency cut-off of 1 % was used for all autosomal variants, as well as an imputation quality score above 0.3 (N ~ 9.7M SNPs).

5.2.2.4. Genome-wide association analysis (GWAS)

Genotype-phenotype association analyses were conducted using SNPTEST v2.5.1 (Marchini, Howie, Myers, McVean, & Donnelly, 2007). The ‘frequentist 1’ option was used to specify an additive model, and genotype dosages were analysed to account for genotype uncertainty. All phenotypes were adjusted for the following covariates prior to analysis; age, gender, assessment centre, genotyping array and batch and the first 10 genetic principal components for population stratification. The GWAS of VNR has been performed previously (G. Davies et al., 2016b).

5.2.2.5. SNP-based heritability and genetic correlations

Univariate GCTA-GREML (J. Yang et al., 2010) analysis was performed to estimate the proportion of variance explained by all genotyped common SNPs for TMT A, TMT B and TMT B-A. To include only unrelated individuals, a relatedness cut-off of 0.025 was used in the generation of the genetic relationship matrix. Given the likely difference in reliability between the raw (TMT-A and TMT-B) and difference (TMT B-A) scores (Crocker & Algina, 1986), we undertook a supplementary analysis to compare reliability-weighted heritability estimates (see Supplementary Methods) to provide a clearer comparison of h^2 differences between elements of the TMT. Bivariate GCTA-GREML (J. Yang et al., 2010) and LD score regression (B. K. Bulik-Sullivan et al., 2015) were used to derive genetic correlations between TMT measures and VNR in UK Biobank (G. Davies et al., 2016a). LD score regression was also used to estimate genetic correlations between trail making measures in UK Biobank and trail making part A, trail making part B, general cognitive function, processing speed, and memory from the CHARGE consortium (participants aged 45 years or older) meta-analyses of these cognitive phenotypes (G. Davies et al., 2015b; Debette et al., 2015b; Ibrahim-Verbaas et al., 2016).

5.2.2.6. Gene-based association analysis

MAGMA (de Leeuw, Mooij, Heskes, & Posthuma, 2015) was used to derive gene-based associations using the summary results of the three GWAS for trail making. 18 062 genes were analysed after the SNPs were assigned a gene based on their position using the NCBI 37.3 build, without additional boundaries placed around the genes. To account for linkage disequilibrium, the European 1000 Genomes data panel (phase 1, release 3) was used as a reference. A Bonferroni correction was used to control for 18 062 tests ($\alpha = 0.05/18\,345$; $P < 2.73 \times 10^{-6}$). The gene-based associations for trail making were compared with gene-based associations for VNR, and with the gene-based associations for trail making, general cognitive function, processing speed, and memory from the CHARGE consortium, based on the GWAS summary results (G. Davies et al., 2015a; Debette et al., 2015a; Ibrahim-Verbaas et al., 2016). The CHARGE summary results were converted from HapMap2 to 1000G format to ensure the maximum overlap between the two samples. This was achieved using the LiftOver program, which converts coordinate ranges between genome assemblies.

5.2.2.7. Partitioned heritability

Partitioned heritability analyses were performed on the trail making SNP-based association results to determine if SNPs group together according to a specific biological function or role and thereby making an enriched contribution to the total proportion of heritability of the trail making phenotypes. These analyses were performed using the data processing pipeline as suggested by Finucane et al. (Finucane et al., 2015).

5.2.2.8. Polygenic profile analyses

Polygenic profile analyses were performed to predict trail making test performance into UK Biobank and to predict cognitive function scores in two independent cohorts, Generation Scotland's Scottish Family Health Study (GS) and the Lothian Birth Cohort of 1936

(LBC1936). Prediction from the CHARGE consortium meta-analysis of trail making, general cognitive function, processing speed, and memory into UK Biobank was performed to test the extent to which individual differences in trail making tests in UK Biobank could be predicted by the polygenic architecture of these four traits.

Polygenic prediction into UK Biobank.

The UK Biobank genotyping data were recoded from numeric (1,2) allele coding to standard ACGT coding using a bespoke programme developed by one of the present authors (DCL) (Hagenaars et al., 2016b). Polygenic profile scores were created for trail making part A, trail making part B, general cognitive function, processing speed, and memory based on the results from the CHARGE consortium meta-analysis in all genotyped participants using PRSice (Euesden, Lewis, & O'Reilly, 2015). SNPs with a minor allele frequency < 0.01 were removed prior to creating the scores. Clumping was used to obtain SNPs in linkage disequilibrium with an $r^2 < 0.25$ within a 250kb window. Five polygenic profiles were created for each of the three phenotypes according to the significance of the association with the trail making phenotype, at p-value thresholds of 0.01, 0.05, 0.1, 0.5 and 1 (all LD pruned SNPs). Regression models were used to examine the association between the polygenic profiles and TMT A, TMT B and TMT B-A phenotype scores in UK Biobank, adjusting for age at measurement, sex, genotyping batch and array, assessment centre, and the first ten genetic principal components for population stratification. All associations were corrected for multiple testing using the false discovery rate (FDR) method (Benjamini & Hochberg, 1995).

Polygenic prediction into GS and LBC1936.

Polygenic profile scores were created in PRSice (Euesden et al., 2015), using the UK Biobank trail making SNP-based association results, for genotyped participants of GS ($n = 19\,994$, mean (SD) age = 47.18 (15.10) years) and LBC1936 ($n = 1005$, mean (SD) age of 72.55 (0.7) years for all tests except trail making part B which was tested at a mean (SD) age of 76.30

(0.68) years). Individuals were removed from GS if they had contributed to both UK Biobank and GS ($n = 174$). Polygenic profile scores were created based on the significance of the association in UK Biobank with the trail making phenotype, at p-value thresholds of 0.01, 0.05, 0.1, 0.5 and 1 (all SNPs). Linear regression models were created to test the association between the polygenic profiles for trail making and the target phenotypes in: GS (Wechsler digit-symbol substitution (Wechsler, 1997a), phonemic verbal fluency (Lezak et al., 2004), Wechsler logical memory (Wechsler, 1997b), the Mill Hill vocabulary test (Raven & Court, 1993), a fluid cognitive function component, and a general cognitive function component); and LBC1936 (trail making part B, a fluid cognitive function component, vocabulary, memory, processing speed, change in fluid cognitive function between age 11 and age 70, Moray House Test score at age 11, and Moray House Test score at age 70). Further details about the cognitive tests can be found in the Supplementary Materials. All models were adjusted for age, sex and the first five (GS) or four (LBC1936) principal components for population stratification. The GS models were also adjusted for family structure by fitting a univariate linear mixed model which estimates the genetic and environmental variance, using the ASReml program (Gilmour, Gogel, Cullis, Thompson, & Butler, 2009). All associations were corrected for multiple testing using the FDR method (Benjamini & Hochberg, 1995).

5.2.2.9. Meta-analysis

Inverse variance-weighted meta-analysis of UK Biobank trail making and CHARGE trail making GWAS was performed using the METAL package (<http://www.sph.umich.edu/csg/abecasis/Metal>). The meta-analysis was restricted to SNPs that were available in both samples (N SNPs TMT A = 2,332,746; N SNPs TMT B = 2,466,810), and the samples did not include any overlapping individuals. The total sample in the meta-analysis consisted of 29,251 individuals for TMT A and 30,022 for TMT B.

5.2.3. Results

5.2.3.1. Phenotypic correlations

23,822 individuals with genetic data completed TMT A, 23,812 individuals with genetic data completed TMT B, and 23,769 individuals with genetic data had complete information for TMT B-A. Table 5-1 shows the phenotypic correlations between the TMT phenotypes, as well as with verbal-numerical reasoning in UK Biobank. Correlations indicated that individuals who took more time to complete the trail making tests had lower performance on the verbal-numerical reasoning test. The strongest correlation between VNR and TMT was found for TMT B (0.36). Supplementary Figure 2 shows the age and sex distribution of the different trail making measures.

Table 5-1. Phenotypic correlations for the UK Biobank cognitive tests in all genotyped participants. Standard errors for the correlations are shown in parentheses. Pearson correlations were used for continuous-continuous correlations for the phenotypic correlations.

	TMT A	TMT B	TMT B-A	VNR
TMT A	-			
TMT B	0.62 (0.004)	-		
TMT B-A	0.04 (0.006)	0.80 (0.002)	-	
VNR	0.20 (0.010)	0.36 (0.009)	0.32 (0.010)	-

TMT A, trail making part A; TMT B, trail making part B; TMT B-A, trail making part B – part A; VNR, verbal-numerical reasoning.

5.2.3.2. Genome-wide association study

The results of the GWAS analyses are presented in Figure 5-2; for each trail making phenotype a Manhattan and a QQ plot is shown.

Trail making test part A

For TMT A no SNPs reached genome-wide significance. Gene based analyses identified three genes that were significantly associated with TMT A (Table 5-2 and Supplementary Table 1a); *CRNKL1*, a protein necessary for pre-mRNA splicing on chromosome 20 (Chung et al., 2002); caspase 5 (*CASP5*), which plays a role in the execution phase of cell apoptosis on chromosome

11 (Earnshaw, Martins, & Kaufmann, 1999); and *NAA20*, a component of the N-acetyltransferase complex B on chromosome 20 (Starheim et al., 2008). All three of these genes were also nominally significant ($p < 0.05$) in the GWAS of TMT B, and *CASP5* was also nominally significant in the analyses for CHARGE general cognitive function and processing speed (Table 5-2).

The proportion of variance in TMT A explained by all common genetic variants using GCTA-GREML was 0.079 (SE 0.024).

Trail making test part B

One SNP exhibited genome-wide significance for TMT B, on chromosome 1 (rs34804445, $p = 4.18 \times 10^{-8}$, MAF = 0.0253). This SNP was not located within a gene. Gene based analyses identified one gene (*PUM1* on chromosome 1) associated with TMT B (Table 5-2 and Supplementary Table 1b); this gene regulates ATAXIN1, and is associated with neurodegeneration (Gennarino et al., 2015). This gene was also nominally significant ($p < 0.05$) in the gene-based analysis for the other trail making variables measured in UK Biobank. Results for this gene were not available for the CHARGE consortium phenotypes (Table 5-2).

The proportion of variance in TMT B explained by all common genetic variants using GCTA-GREML was 0.224 (SE 0.026).

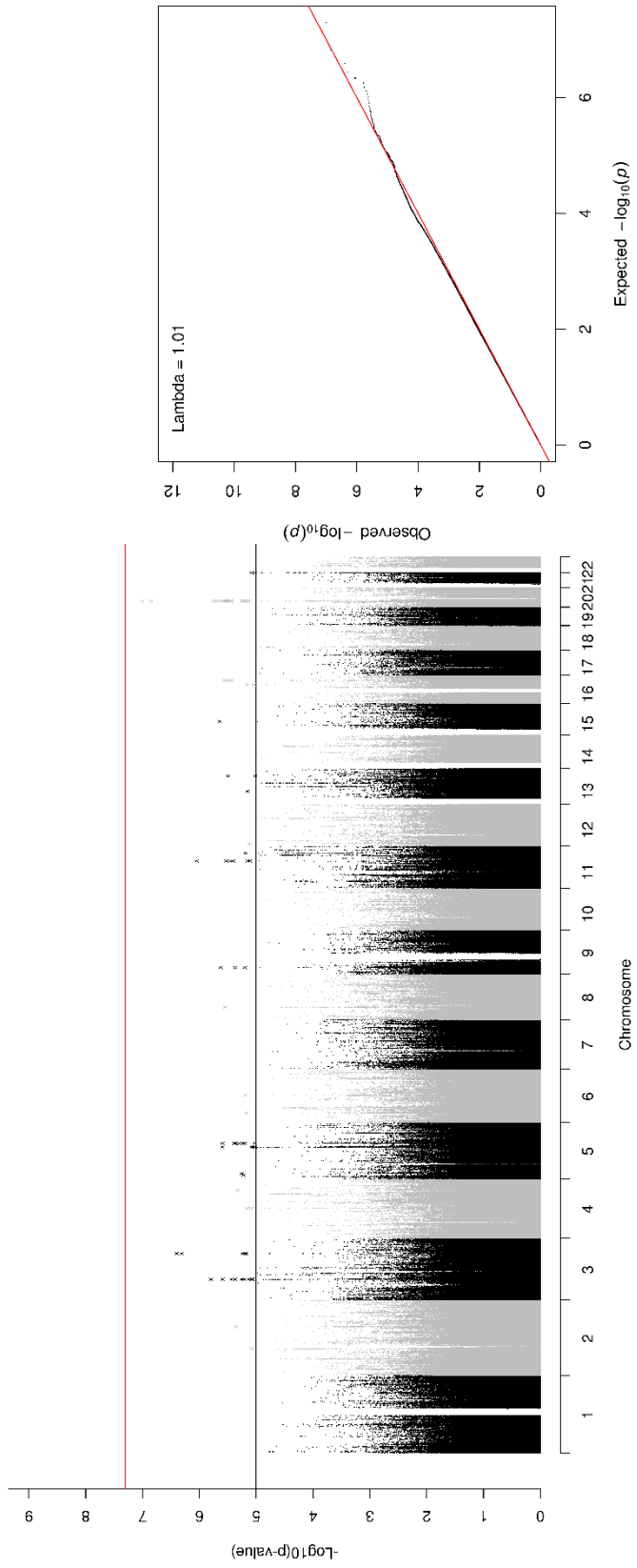
Trail making test part B – part A

No SNPs reached genome-wide significance for TMT B-A. Gene-based analyses did not identify any significant associations for TMT B-A (Supplementary Table 1c).

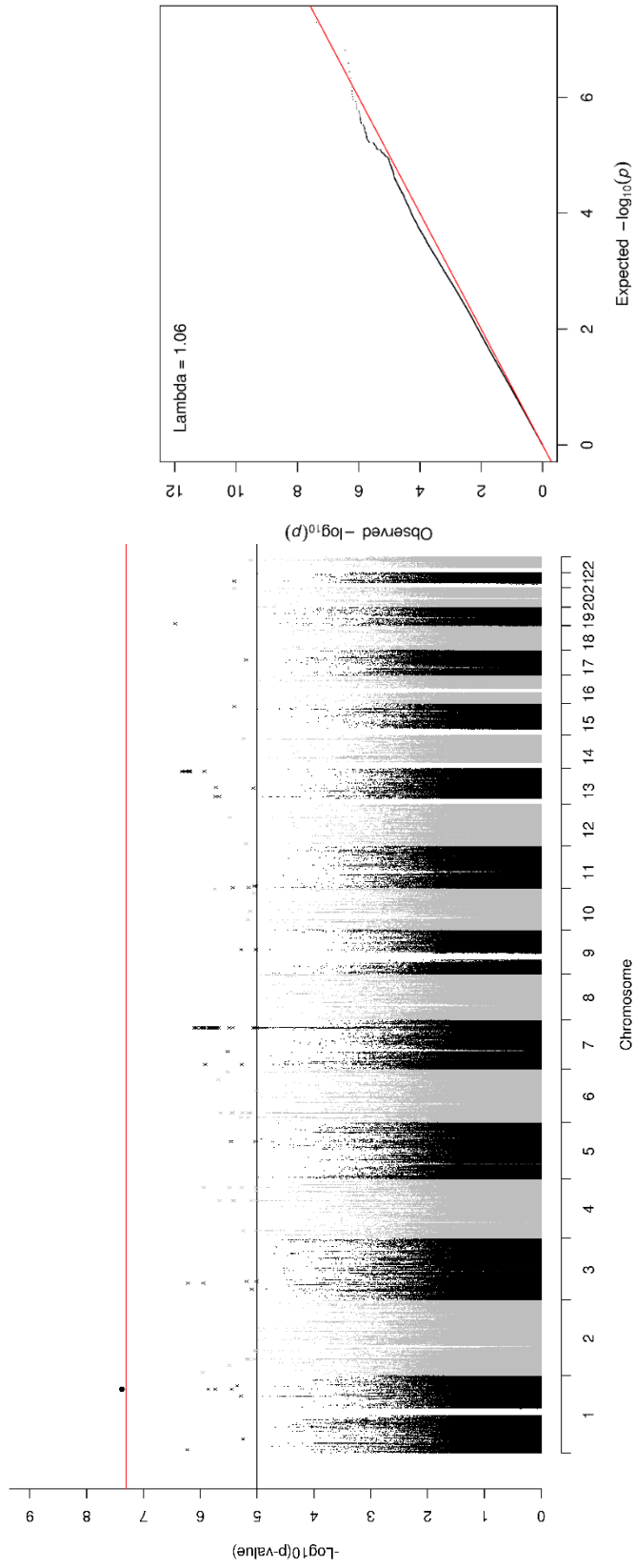
The proportion of variance in TMT B-A explained by all common genetic variants using GCTA-GREML was 0.176 (SE 0.025). Heritability estimates and standard errors of all three

TMT measures, weighted according to estimates of their reliabilities, are reported in Supplementary Table 2. They indicate that the ostensible difference in h^2 between TMT-B and TMT B-A could possibly be attributed to differences in reliability.

Trail Making Part A



Trail Making Part B



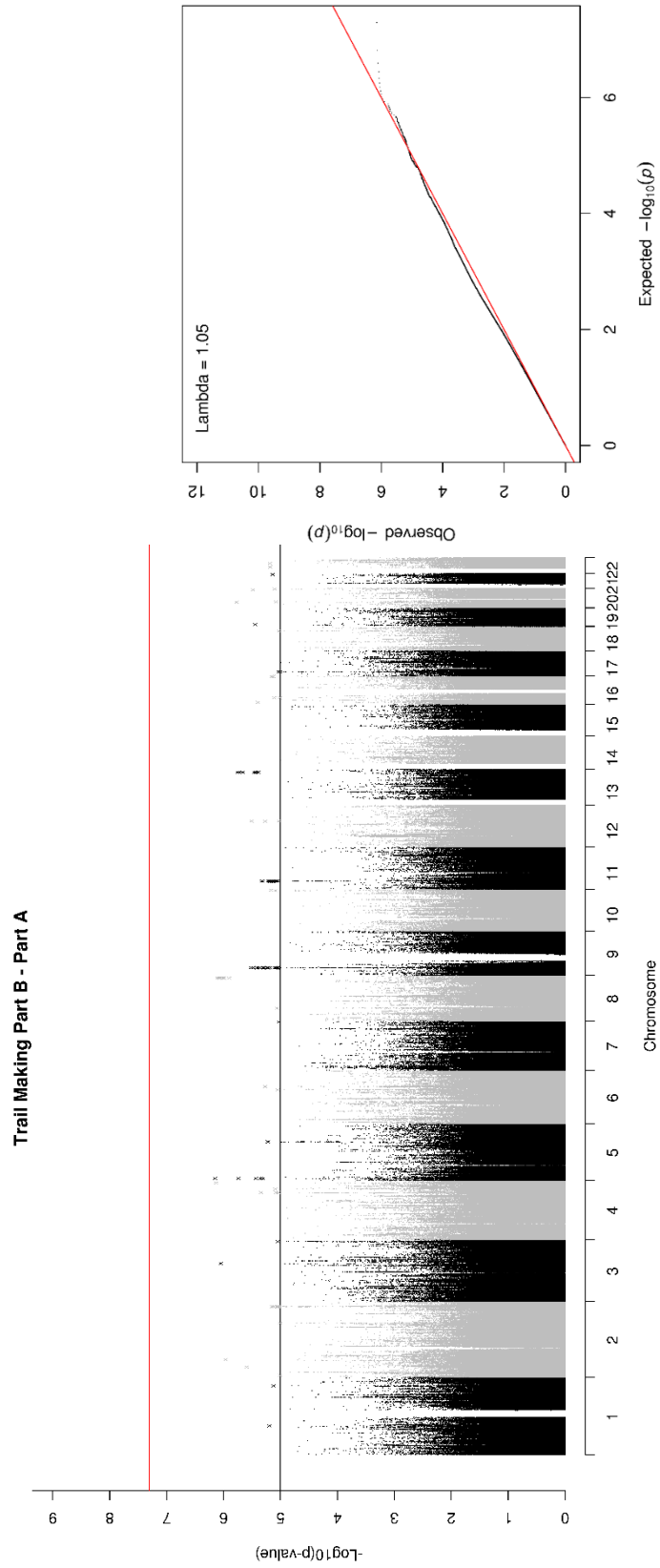


Figure 5-2. Manhattan and Q-Q plot of P-values of the SNP-based association analysis of Trail Making Part A, Trail Making Part B and Trail Making Part B – Part A. The red line in the Manhattan plots indicates the threshold for genome-wide significance ($P < 5 \times 10^{-8}$); the grey line indicates the threshold for suggestive significance ($P < 1 \times 10^{-5}$).

Table 5-2. Shows the genome wide significant genes ($P < 2.73 \times 10^{-6}$) from the UK Biobank trail making phenotypes and the significance values for the same genes using the other two trail making phenotypes and Verbal Numerical Reasoning (VNR) measured in UK Biobank, and cognitive phenotypes from the CHARGE consortium. Unmodified P-values are shown for all phenotypes. TMT A, trail making part A; TMT B, trail making part B; TMT B-A, trail making part B – part A.

CHARGE consortium phenotypes										
UK Biobank phenotypes										
GENE	CHR	TMT A	TMT B	TMT B-A	VNR	TMT A	TMT B	General		
								cognitive function	Processing speed	Memory
<i>CRNKL1</i>	20	2.94×10^{-7}	0.0009	0.3764	0.0433	0.9802	0.7963	0.3308	0.78394	0.21709
<i>CASP5</i>	11	2.06×10^{-6}	0.0105	0.7079	0.6030	0.0909	0.5916	0.0116	0.033069	0.89279
<i>NAA20</i>	20	1.84×10^{-6}	0.0033	0.5590	0.1628	0.9266	0.7289	0.2176	0.62509	0.43073
<i>PUM1</i>	1	0.0413	4.92×10^{-8}	9.03×10^{-5}	0.9461	NA	NA	NA	NA	NA

5.2.3.3. Partitioned heritability

Significant enrichment was found for TMT B in evolutionary conserved regions with a 500bp boundary, where 33% of the SNPs accounted for 95% of the heritability (enrichment metric = 2.85, SE = 0.44, $p = 2.42 \times 10^{-5}$). TMT A and TMT B-A were unsuitable for this analysis, due to low heritability Z-scores, which were 2.6 and 5.4 respectively (Finucane et al., 2015).

5.2.3.4. Genetic correlations

The results of the bivariate GCTA-GREML and LD score regression analyses within UK Biobank are shown in Table 5-3. The LD score regression analyses with the cognitive phenotypes from the CHARGE consortium are shown in Table 5-4. Strong positive genetic correlations, using GCTA-GREML, were observed between all three measures derived from the trail making test in UK Biobank (r_g between 0.64 and 0.96). Large genetic correlations were found between the three trail making tests and verbal-numerical reasoning (r_g between 0.59 and 0.64). Similar results were found when calculating the genetic correlations using LD score regression (Table 5-3). Positive genetic correlations were observed between trail making in UK Biobank and the following GWAS meta-analyses from the CHARGE consortium: general cognitive function (r_g between 0.61 and 0.70), processing speed (r_g between 0.69 and 0.76), and memory (r_g between 0.29 and 0.35) (Table 5-4). The confidence interval for the associations between TMT and general cognitive function, and between TMT and processing speed did not overlap with the confidence interval for the association between TMT and memory.

Table 5-3. Genetic correlations (standard errors) using GCTA-GREML (under diagonal) and LD score regression (above diagonal) for the trail making tests and verbal-numerical reasoning in UK Biobank. TMT A, trail making part A; TMT B, trail making part B; TMT B-A, trail making part B minus trail making part A; VNR, verbal-numerical reasoning.

	TMT A	TMT B	TMT B-A	VNR
TMT A	-	0.921 (0.07)	0.827 (0.17)	0.558 (0.11)
TMT B	0.840 (0.09)	-	0.981 (0.03)	0.767 (0.07)
TMT B-A	0.640 (0.19)	0.958 (0.03)	-	0.793 (0.10)
VNR	0.589 (0.36)	0.636 (0.14)	0.587 (0.18)	-

Table 5-4. Genetic correlations (standard error), derived using LD score regression, between three trail making test in UK Biobank and general cognitive function, processing speed, and memory from the CHARGE consortium. TMT A, trail making part A; TMT B, trail making part B; TMT B-A, trail making part B – part A. Tests that survived FDR correction ($p = 0.0404$) are shown in bold.

	TMT A			TMT B			TMT B-A		
	r_g	SE	p	r_g	SE	p	r_g	SE	p
General cognitive function	0.6076	0.11	2.73×10^{-8}	0.6951	0.07	3.02×10^{-22}	0.6566	0.08	9.84×10^{-15}
Processing speed	0.7614	0.15	3.01×10^{-7}	0.7646	0.08	7.69×10^{-20}	0.6877	0.10	8.36×10^{-13}
Memory	0.2945	0.14	0.0404	0.3532	0.09	0.0001	0.2994	0.11	0.0055

5.2.3.5. Polygenic prediction

Polygenic profiles based on the TMT A summary results from the CHARGE consortium significantly predicted all three trail making tests in UK Biobank (β between 0.016 and 0.029, Table 5-5). Polygenic profiles based on the TMT B summary results from the CHARGE consortium significantly predicted all three trail making tests in UK Biobank (β between 0.024 and 0.036, Table 5-5). The strongest associations for the other cognitive test polygenic profiles (general cognitive function, processing speed, and memory) were found for general cognitive function polygenic profiles predicting TMT B in UK Biobank, explaining 0.67% of the variance. The full results including all thresholds can be found in Supplementary Table 3a.

Table 5-5. Associations between polygenic profiles based on CHARGE cognitive tests and trail making in UK Biobank. FDR correct p-value = 0.04455473. Associations are scored such that a higher polygenic score indicates better performance on the TMT tests.

Phenotypes in UK Biobank													
	Trail making test part A				Trail making test Part B				Trail making test part B – part A				
	best				best				best				
	thres				thres				thres				
	hold	beta	r2%	p	hold	beta	r2%	p	hold	beta	r2%	p	
	hold	beta	r2%	p	hold	beta	r2%	p	hold	beta	r2%	p	
Trail making													
test part A	0.5	0.021	0.04	0.0006	0.5	0.029	0.08	1.34×10⁻⁶	0.5	0.016	0.03	0.0108	
Trail making													
test Part B	1	0.027	0.08	7.36×10⁻⁶	0.5	0.036	0.13	2.07×10⁻⁹	0.1	0.024	0.06	0.0001	
Polygenic													
profiles													
General													
cognitive													
function	0.5	0.058	0.30	2.44×10⁻¹⁹	0.5	0.087	0.67	3.11×10⁻⁴³	0.5	0.065	0.38	1.49×10⁻²²	
Processing													
speed	0.5	0.048	0.22	1.45×10⁻¹⁴	0.5	0.077	0.57	2.60×10⁻³⁷	0.5	0.062	0.37	4.34×10⁻²²	
Memory	0.05	0.020	0.04	0.0011	1	0.034	0.12	9.31×10⁻⁹	1	0.030	0.09	2.32×10⁻⁶	

The GWAS results for the three trail making phenotypes in UK Biobank were used to create polygenic profile scores in two independent cohorts; Generation Scotland (GS), and the Lothian Birth Cohort of 1936 (LBC1936) (Figure 5-3 and Supplementary Tables 3b and 3c). The polygenic profiles for TMT A significantly predicted digit-symbol substitution, verbal fluency, Mill Hill vocabulary, fluid cognitive function, and general cognitive function in GS (β between 0.018 and 0.039). In the LBC1936, the polygenic profiles for TMT A significantly predicted trail making part B ($\beta = 0.102$), fluid cognitive function, memory and change in fluid cognitive function (β between 0.079 and 0.094). Significant predictions were observed across almost all thresholds for TMT B and TMT B-A for the cognitive phenotypes measured in GS. In LBC1936, polygenic profiles for TMT B and TMT B-A were both significantly associated with fluid cognitive function, processing speed, cognitive function at age 11 and cognitive function at age 70. TMT B was also significantly associated with trail making part B, memory and change in fluid cognitive function between age 11 and age 70. The strongest association in GS was found between the polygenic profile for TMT B and Wechsler digit symbol substitution; this association explained 0.53% of the variance, at a SNP inclusion threshold of all SNPs from the GWAS. The largest proportion of variance explained in LBC1936 was 1.75% for trail making part B using the TMT B polygenic score with a SNP inclusion threshold of all SNPs from the GWAS. The complete results can be found in Supplementary Tables 3b and 3c.

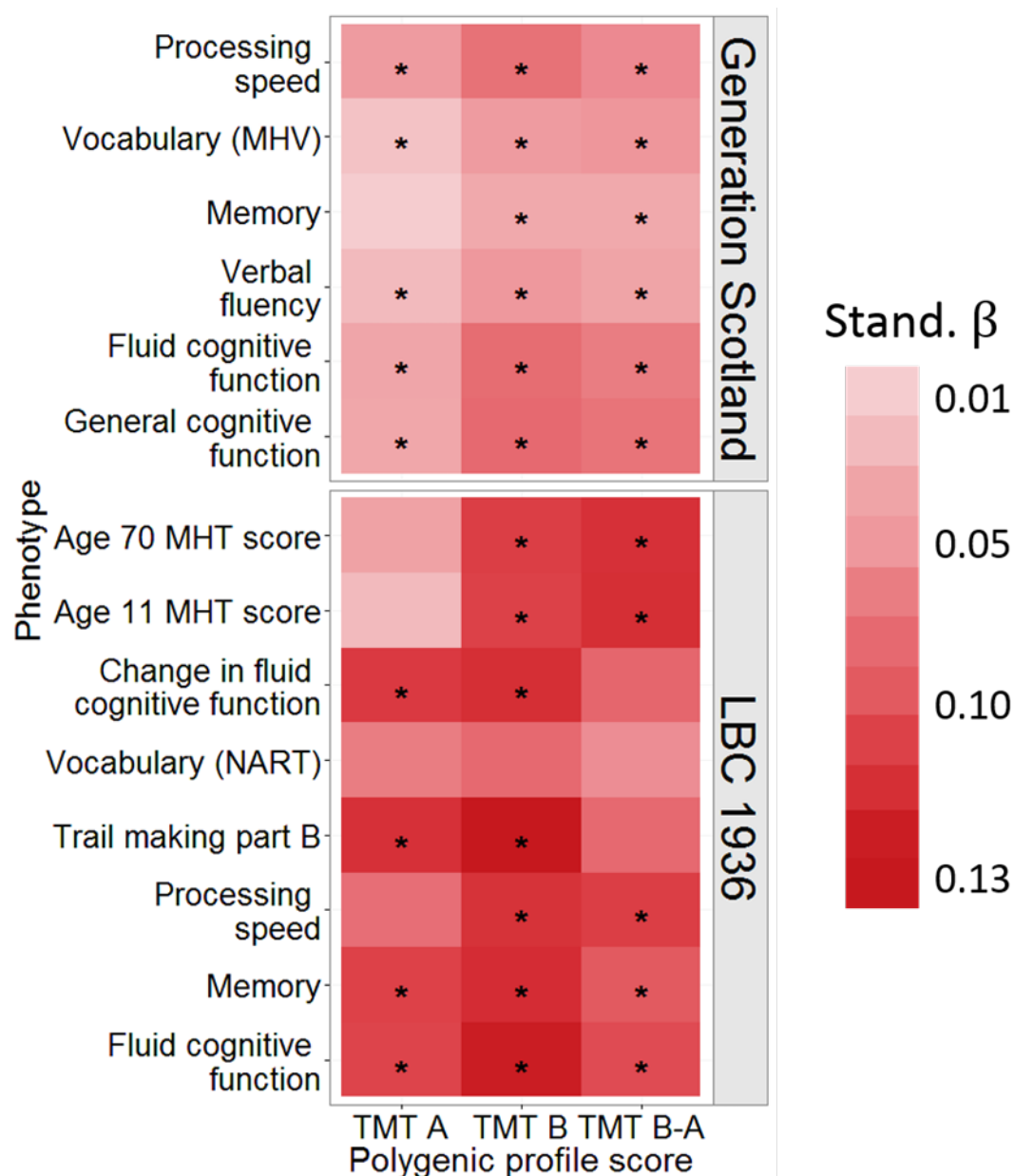


Figure 5-3. Heat map of associations between the polygenic profile scores for trail making in UK Biobank and cognitive function in Generation Scotland and the Lothian Birth Cohort 1936 (LBC 1936). * indicates FDR corrected significant associations (FDR corrected p-value \leq 0.029 (Generation Scotland) or 0.025 (LBC 1936)). Further information can be found in Supplementary Tables 2b and 2c.

5.2.3.6. Meta-analysis

In the meta-analysis of the combined dataset (UK Biobank and CHARGE, combined N TMT A = 29,251, combined N TMT B = 30,022), no genome-wide significant SNPs were observed

for TMT A or TMT B (Supplementary Figure 3). The one genome-wide significant hit identified in this study for TMT B was not available in CHARGE.

5.2.4. Discussion

This study finds one genome-wide significant variant associated with trail making test part B performance in UK Biobank, and provides the first SNP-based heritability estimates for the three widely-used TMT measures. We identified high genetic correlations between trail making, verbal-numerical reasoning, general cognitive function, and processing speed, and somewhat lower genetic correlations with memory. Using only common SNPs to create a polygenic score for TMT B, we were able, at best, to predict ~2% of the variance in trail making part B in LBC1936. Taken together, these analyses point to a considerable degree of shared polygenic architecture for TMT performance with general cognitive function and processing speed measures, in particular. The results are consistent with the hypothesis that trail making is genetically and phenotypically similar to general fluid cognitive function (T. Lee et al., 2012; Salthouse, 2011a, 2011b).

Univariate GCTA-GREML analyses suggested SNP-based heritability estimates for TMT A, TMT B and TMT B-A of 8%, 22% and 18% respectively. These provide a first estimate of the contribution of common SNPs to the phenotype of trail making and suggest that common SNPs account for around half of the additive genetic variation for trail making, based on twin and family studies (Vasilopoulos et al., 2012). SNP-based heritability studies for other complex traits also report similar differences between SNP based and pedigree based heritability (G. Davies et al., 2011; Jian Yang et al., 2010). Twin and family studies estimate heritability based on all causal variants, both common and rare, whereas SNP-based studies estimate heritability only on genotyped SNPs in LD with causal variants. It is possible that causal variants have lower minor allele frequencies than the genotyped SNPs, leading to incomplete LD between unknown causal variants and genotyped SNPs (Visscher, Yang, & Goddard, 2010).

Previous studies of the genetic overlap between trail making and other cognitive abilities have shown genetic overlap between trail making and general cognitive function using a twin design (T. Lee et al., 2012; Vasilopoulos et al., 2012). Our results add to this by using a molecular genetic design and showing shared genetic aetiology between trail making and verbal numerical reasoning in UK Biobank, as well as with general cognitive function, processing speed, and memory from the CHARGE consortium. The estimates of the genetic correlations within UK Biobank were similar for both GCTA-GREML and LDS regression, suggesting that these results are unlikely to constitute false positives.

We also used polygenic profile scores to estimate the genetic overlap between TMT and other cognitive abilities. First we created polygenic profiles based on the CHARGE consortium summary GWAS data (including trail making, general cognitive function, processing speed, and memory) and found that the polygenic profile for general cognitive function was the best predictor of all TMT scores in UK Biobank compared to either of the other polygenic profiles. All estimates were small ($< 1\%$ of variance was accounted for), but should be considered the minimum estimate of the variance explained. The polygenic profile method prunes SNPs in LD and assumes that a single causal variant is tagged in each LD block. If that assumption is violated, the proportion of variance explained will be underestimated. Nevertheless, the unequal sample sizes from which the polygenic profile scores were derived (TMT ~ 6000; general cognitive function ~54,000; processing speed ~ 32,000, memory ~ 29,000) may have led to an underestimation of the ability of CHARGE TMT score to predict UK Biobank TMT test performance.

The genetic association between TMT and other cognitive measures could be due to an overall halo-effect of general cognitive ability. While the current study does not allow us to test this empirically, we note that the respective polygenic associations between TMT and fluid cognitive ability in GS and LBC1936, as well as the genetic correlations between TMT and

verbal-numerical reasoning, do point to this halo-effect. Future studies could expand these findings by removing the variance specific to a latent measure of general cognitive ability (measured using ≥ 3 tests from different cognitive domains) from the associations between TMT and other measures of cognitive ability.

Our combined meta-analysis of UK Biobank and CHARGE trail making did not yield any significant SNPs. This could be ascribed to the following factors. The SNPs for the CHARGE consortium are imputed to the HAPMAP 2 reference panel ($N \sim 2M$ SNPs) whereas the UK Biobank sample is imputed to a combination of the UK10 haplotype and the 1000G reference panel ($N \sim 17M$ SNPs). For TMT A, 2 332 746 SNPs overlapped between UK Biobank and CHARGE, and for TMT B, 2 466 810 SNPs overlapped between the two samples. The SNP that reached genome-wide significance in the UK Biobank GWAS was not available in CHARGE.

In addition to those discussed above, our study has other limitations. There are currently no reliability data available for the TMT version administered in UK Biobank. Though the computer-based version was based upon standard administration protocols, the current absence of such data necessitates that these results be interpreted with appropriate caution. The measure of fluid cognitive function provided by UK Biobank (which we have called verbal-numerical reasoning) showed a relatively modest age-related trajectory, in contrast to the steeper and well-replicated age-related decline that would be expected for this construct (Salthouse, 2004; Tucker-Drob, 2009) (Supplementary Figure 4). This may partly explain the relatively modest correlation of verbal-numerical reasoning with TMT performance, when compared to those previously reported (Salthouse, 2011b) and may have also had a bearing on our analyses of genetic overlap within UK Biobank. In addition, the UK Biobank sample did not have sufficient breadth of contemporaneously-administered standardised/validated cognitive tests to be able to construct a robust measure of general cognitive function (such as

in other large samples(Ritchie et al., 2016; Salthouse, 2011a, 2011b)). This limited our ability to perform a more detailed analysis of the phenotypic or genetic overlap between trail making and general cognitive function in UK Biobank itself.

This study has several strengths. It has the largest single sample size to date of a GWAS for trail making, offering greater statistical power while excluding bias caused by sample or phenotypic heterogeneity. Population stratification was minimized by only using individuals of white British ancestry. This study shows the first estimates of the heritability for TMT using molecular genetic data, uses a comprehensive battery of techniques to examine genetic architecture of TMT, and used the same trail making test and administration protocol across the whole sample. The use of both GWAS summary data from the CHARGE consortium, and the prediction of the UK Biobank TMT GWAS into GS and LBC1936 cognitive phenotypes allowed a detailed examination of the shared genetic aetiology between TMT and cognitive phenotypes.

These strengths have enabled a detailed characterisation of the shared genetic aetiology between performance on TMT and other cognitive abilities. Our results, spanning methodologies and cohorts, provide strong evidence for a shared genetic aetiology between TMT performance and general cognitive function and processing speed, which are themselves strongly phenotypically and genetically correlated. When the full genetic data from UK Biobank on half a million individuals becomes available, it would enable robust replication and extensions of the current findings. More detailed cognitive testing is planned for UK Biobank, and these data can be used in future studies to further examine the genetic overlap between TMT and other cognitive functions.

5.2.5.Acknowledgments

This research was conducted using the UK Biobank Resource. The work was undertaken in The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1); funding from the BBSRC and Medical Research Council (MRC) is gratefully acknowledged. The Lothian Birth Cohort is supported by Age UK (Disconnected Mind Project). AMM and IJD are supported by a Wellcome Trust Strategic Award (104036/Z/14/Z).

5.2.6. Conflict of Interest

IJD is a participant in UK Biobank.

5.3. Conclusion

This Chapter set out to investigate the genetic architecture of the Trail Making Test and its overlap with other domains of cognitive ability. Up to 22% of the variance in the Trail Making Test is explained by common genetic influences. Of the modest phenotypic association between TMT and verbal-numerical reasoning in UK Biobank, around 70% is due to common genetic influences. Similar estimates were found for the genetic correlation between TMT and general cognitive ability and processing speed. PRS analysis also indicated extensive shared genetic aetiology between TMT, general cognitive ability and processing speed. Some overlap was found with memory; however, these estimates were much smaller. More broadly, these results highlight the complex pathways with cognitive ability, and might in, future research, aid to the understanding of association between cognitive ability and health. Together with Chapter 4, the current Chapter focussed on cognitive ability and its overlap with health outcomes. As described in Chapter 2, personality is a second important trait in the field of individual differences. The following two Chapters will therefore focus on negative emotions and its association with health outcomes, starting with the association between neuroticism and health in Chapter 6, followed by the associations between self-reported tiredness and health in Chapter 7.

6. Genetic overlap between neuroticism and health

6.1. Introduction

The second Section of this thesis, including this Chapter and the next (Chapter 7), will examine the shared genetic aetiology between negative emotions and health. The current Chapter will focus on the personality trait of neuroticism. Neuroticism is partly influenced by genetic factors; behavioural genetic studies have indicated a heritability of around 40% (Vukasović & Bratko, 2015), whereas molecular genetic studies have shown that around 15% of the variance in neuroticism is due to genetic factors (D. J. Smith et al., 2016). Both behavioural and molecular genetic studies have identified some shared genetic aetiology between neuroticism and health, in particular mental health (Kendler & Myers, 2010; Okbay et al., 2016a). Relatively little research has been performed to quantify the extent of the genetic association between neuroticism and health traits using molecular genetic techniques. This Chapter will examine the shared genetic aetiology between neuroticism and mental and physical health in UK Biobank. This study has been published in *Translational Psychiatry* and is included in full in Section 6.2.

**6.2. Pleiotropy between neuroticism and physical and mental health:
findings from 108 038 men and women in UK Biobank**

ORIGINAL ARTICLE

Pleiotropy between neuroticism and physical and mental health: findings from 108 038 men and women in UK Biobank

CR Gale^{1,2,3,9}, SP Hagenaars^{1,2,4,9}, G Davies^{1,2}, WD Hill^{1,2}, DCM Liewald^{1,2}, B Cullen⁵, BW Penninx⁶, International Consortium for Blood Pressure GWAS, CHARGE Consortium Aging and Longevity Group, DI Boomsma⁷, J Pell⁵, AM McIntosh⁴, DJ Smith⁵, IJ Deary^{1,2,10} and SE Harris^{1,8,10}

People with higher levels of neuroticism have an increased risk of several types of mental disorder. Higher neuroticism has also been associated, less consistently, with increased risk of various physical health outcomes. We hypothesised that these associations may, in part, be due to shared genetic influences. We tested for pleiotropy between neuroticism and 17 mental and physical diseases or health traits using linkage disequilibrium regression and polygenic profile scoring. Genetic correlations were derived between neuroticism scores in 108 038 people in the UK Biobank and health-related measures from 14 large genome-wide association studies (GWASs). Summary information for the 17 GWASs was used to create polygenic risk scores for the health-related measures in the UK Biobank participants. Associations between the health-related polygenic scores and neuroticism were examined using regression, adjusting for age, sex, genotyping batch, genotyping array, assessment centre and population stratification. Genetic correlations were identified between neuroticism and anorexia nervosa ($r_g = 0.17$), major depressive disorder ($r_g = 0.66$) and schizophrenia ($r_g = 0.21$). Polygenic risk for several health-related measures were associated with neuroticism, in a positive direction in the case of bipolar disorder, borderline personality, major depressive disorder, negative affect, neuroticism (Genetics of Personality Consortium), schizophrenia, coronary artery disease, and smoking (β between 0.009–0.043), and in a negative direction in the case of body mass index ($\beta = -0.0095$). A high level of pleiotropy exists between neuroticism and some measures of mental and physical health, particularly major depressive disorder and schizophrenia.

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INTRODUCTION

There is considerable evidence that the personality trait of neuroticism¹—which describes stable individual differences in the tendency to experience negative emotions—has profound significance for public health.² People who are higher in neuroticism have an increased risk of developing Axis I psychopathology, especially the common mental disorders such as mood, anxiety, somatoform and substance use disorders, and also schizophrenia, bipolar disorder and attention-deficit hyperactivity disorder (ADHD).^{3–6} Higher neuroticism is associated with increased likelihood of diagnosis with Axis II personality disorders⁷ and with greater comorbidity between internalising disorders (such as major depression, generalised anxiety, panic disorders and phobias) and externalising disorders (such as alcohol and drug dependence, antisocial personality and conduct disorders).⁸ There is evidence that higher neuroticism is linked with risk of developing Alzheimer's disease.⁹ People who are higher in neuroticism tend to make greater use of mental health services, regardless of whether they have a mental disorder,¹⁰ perhaps because they are more likely to perceive a need for care.¹¹ The

estimated economic costs of neuroticism in terms of health-care use and absenteeism are massive.¹² Much of these costs relate to reported chronic somatic conditions.¹² Higher neuroticism has been linked with increased somatic complaints,^{13,14} with perception of poorer health,^{15,16} with future somatic multi-morbidity, as assessed by a count of reported chronic conditions,¹⁷ and with increased likelihood of reporting a range of physical health problems.¹⁸

Evidence that neuroticism is predictive of objectively assessed physical health is still relatively sparse and findings to date are often mixed. For example, whereas some prospective studies have found that higher neuroticism increases mortality from all causes¹⁹ or coronary heart disease,²⁰ and is predictive of raised blood pressure²¹ or body mass index (BMI),²² others have found no such association.^{23–26} In a pooled analysis of data from five cohorts, there was no consistent association between neuroticism and incidence of type 2 diabetes: higher neuroticism was linked with increased risk in one cohort, but not in others.²⁷

Part of the explanation for associations between neuroticism and these various mental and physical health outcomes may be

¹Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK; ²Department of Psychology, University of Edinburgh, Edinburgh, UK; ³MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK; ⁴Division of Psychiatry, University of Edinburgh, Edinburgh, UK; ⁵Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK; ⁶Department of Psychiatry, EMGO Institute for Health and Care Research and Neuroscience Campus Amsterdam, VU University Medical Center/GGZ inGeest, Amsterdam, The Netherlands; ⁷Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands and ⁸Medical Genetics Section, University of Edinburgh Centre for Genomic and Experimental Medicine and MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK. Correspondence: Professor C Gale, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK.
E-mail: crg@mrc.soton.ac.uk

⁹These authors contributed equally to this work.

¹⁰These authors contributed equally to this work.

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due to shared genetic influences. Twin and adoption studies suggest that genetic influences account for between a third and a half of individual differences in neuroticism.¹ Many physical and mental illnesses and health-related measures also show moderate heritability.²⁸ Twin studies have shown that there is considerable overlap between the genetic factors that influence variations in neuroticism and those that determine risk of depression and other internalising disorders.^{29,30} It is now possible to test for such pleiotropy in associations between neuroticism and health outcomes using data from single nucleotide polymorphism (SNP) genotyping in unrelated individuals, making it possible to carry out much larger studies without the assumptions made by twin-study methods. A recent genome-wide association meta-analysis based on data from over 70 000 individuals found that neuroticism is influenced by many genetic variants of small effect, that is, a polygenic effect, that also influence the risk of major depressive disorder.³¹ Whether there is pleiotropy between neuroticism and other mental disorders or with physical health outcomes is unclear.

Testing for pleiotropy using SNP-based genetic data can be carried out in several ways. Linkage disequilibrium (LD) regression calculates genetic correlations between health measures using the summary results of genome-wide association studies (GWASs).³² It determines how much of the genetic influence on two traits/diseases is common to both. Polygenic risk scoring³³ uses summary GWAS data for a given illness or health trait to test whether polygenic liability to that illness/trait is associated with phenotypes for that illness/trait (for example, neuroticism scores) or others measured in an independent sample. It allows the amount of variance in one trait/disease attributed to the polygenic score for a second trait/disease to be calculated. Polygenic risk of neuroticism was recently associated with major depressive disorder.³¹

In the present study we aimed to discover whether shared genetic aetiology explains part of the associations between neuroticism and various physical and mental health outcomes, all of which have been shown to be phenotypically correlated with neuroticism in at least one study. We used data on over 108 000 UK Biobank participants who completed a questionnaire on neuroticism and provided DNA for genome-wide genotyping. Using summary data from GWAS meta-analyses on 17 health-related measures, we tested for neuroticism-health pleiotropy using two complementary methods. First, we used LD score regression to derive genetic correlations between health-related measures and neuroticism. Second, we calculated the associations between polygenic risk scores for health-related measures and the neuroticism phenotype in UK Biobank participants.

MATERIALS AND METHODS

Participants

The participants in this study took part in the baseline survey of UK Biobank.³⁴ (<http://www.ukbiobank.ac.uk>). UK Biobank was set up as a resource for identifying determinants of disease in middle-aged and older people. Between 2006 and 2010, 502 655 community-dwelling people aged between 37 and 73 years and living in the United Kingdom were recruited to the study. They underwent assessments of cognitive and physical functions, mood and personality. They provided blood, urine and saliva samples for future analysis, completed questionnaires about their social backgrounds and lifestyle and agreed to have their health followed longitudinally. UK Biobank received ethical approval from the Research Ethics Committee (REC reference 11/NW/0382).

For the present study, genome-wide genotyping data were available on 112 151 individuals (58 914 female) aged 40–73 years (mean age = 56.9 years, s.d. = 7.9) after the quality control process (see below).

Procedures

Neuroticism. Participants completed the Neuroticism scale of the Eysenck Personality Questionnaire-Revised (EPQ-R) Short Form.³⁵ This scale has been concurrently validated in older people against two of the most

widely used measures of neuroticism, taken from the International Personality Item Pool (IPIP) and the NEO-Five Factor Inventory (NEO-FFI); it correlated – 0.84 with the IPIP-Emotional Stability scale and 0.85 with the NEO-FFI Neuroticism scale.³⁶ A previous study found a high genetic correlation (0.91) between the EPQ-R Short Form Neuroticism scale and psychological distress assessed in a non-psychiatric population using the 30-item General Health Questionnaire.³⁷

Genotyping and quality control. In all, 152 729 UK Biobank blood samples were genotyped using either the UK BiLEVE³⁸ array ($N = 49\,979$) or the UK Biobank axiom array ($N = 102\,750$). A full description of the genotyping process is available in the Supplementary Materials. Quality control was performed by Affymetrix (Santa Clara, CA, USA), the Wellcome Trust Centre for Human Genetics and by the present authors; this included removal of participants based on missingness, relatedness, gender mismatch, non-British ancestry and other criteria, and is described in the Supplementary Materials.

Genome-wide association analyses in the UK Biobank sample. Genome-wide association analyses were performed on the neuroticism measure in order to use the summary results for LD regression. Details of the GWAS procedures are provided in the Supplementary Materials. Results from the GWAS are published elsewhere.³⁹

Curation of summary results from GWAS consortia on health-related variables. In order to conduct LD score regression and polygenic profile score analyses between the UK Biobank neuroticism data and the genetic predisposition to mental and physical health outcomes, we gathered summary data from published meta-analyses on 17 health-related measures: 9 relating to mental health (ADHD, Alzheimer's disease, anorexia nervosa, bipolar disorder, borderline personality, major depressive disorder, negative affect, neuroticism (from the Genetics of Personality Consortium (GPC)) and schizophrenia) and 8 relating to physical health (systolic and diastolic blood pressure, BMI, coronary artery disease, longevity, rheumatoid arthritis, smoking status and type 2 diabetes). Details of these health-related variables, the consortia's websites, key references and number of subjects included in each consortium's GWAS are given in Supplementary Table 1.

Statistical analysis

Computing genetic associations between neuroticism and health-related variables. We use two methods to compute genetic associations between neuroticism and the health-related variables, LD score regression and polygenic profile/risk scoring. Each provides a different metric to infer the existence of pleiotropy between pairs of traits. LD score regression was used to derive genetic correlations to determine the degree to which the polygenic architecture of a trait overlaps with that of another. Genetic correlations were also derived between the different physical and mental health measures, and neuroticism based on the results of the GWAS from the GPC by de Moor *et al.*³¹ A genetic correlation between the two neuroticism GWAS (UK Biobank and GPC) was also calculated. The polygenic risk score method was used to test the extent to which the polygenic information from GWASs of health-related variables could predict neuroticism in the UK Biobank participants. Both LD score regression and polygenic risk scores are dependent on the traits analysed being highly polygenic in nature, that is, where a large number of variants of small effect contribute towards phenotypic variation.^{32,40} LD score regression was performed between the 14 health-related traits from GWAS consortia, as some measures did not pass thresholds to be included in LD score analysis, while the polygenic profile score analyses were performed on the complete set of 17 health-related traits from GWAS consortia.

LD score regression. In order to quantify the extent of pleiotropy between neuroticism, measured in UK Biobank, and the collated health traits, we used LD score regression.^{32,41} This is a class of techniques that exploits the correlational structure of the SNPs found across the genome (we provide more details of LD score regression in the Supplementary Materials). Here we use LD score regression to derive genetic correlations between neuroticism and health-related measures using 14 large GWAS consortia data sets that enable pleiotropy of their health-related traits to be quantified with the neuroticism trait in UK Biobank. We followed the data-processing pipeline devised by Bulik-Sullivan *et al.*^{32,41} described in more detail in the Supplementary Materials. In order to ensure that the genetic correlation for the Alzheimer's disease phenotype was not driven by a

Table 1. Genetic correlations between neuroticism documented in UK Biobank and mental and physical health-related traits curated from GWAS consortia

Trait Category	Traits from GWAS consortia	Neuroticism (UKB) (n = 108 038)			Neuroticism (GPC) (n = 63 661)		
		r_g	s.e.	P	r_g	s.e.	P
Mental health	ADHD	0.060	0.082	0.4681	0.090	0.191	0.6371
	Alzheimer's disease	0.118	0.080	0.1378	0.089	0.177	0.6147
	Alzheimer's disease (500 kb)	0.091	0.063	0.1514	0.051	0.145	0.7262
	Anorexia nervosa	0.174	0.04	2.36×10^{-5}	0.319	0.082	9.56×10^{-5}
	Bipolar disorder	0.083	0.052	0.1096	0.162	0.101	0.1091
	Major depressive disorder	0.659	0.087	2.75×10^{-14}	1.073	0.199	7.15×10^{-8}
	Schizophrenia	0.212	0.050	2.39×10^{-5}	0.198	0.068	0.0033
Physical health	Blood pressure: diastolic	-0.011	0.078	0.887	-0.108	0.091	0.2363
	Blood pressure: systolic	-0.051	0.060	0.3959	-0.008	0.083	0.925
	BMI	-0.036	0.028	0.1921	0.046	0.055	0.4077
	Coronary artery disease	0.104	0.053	0.0489	0.221	0.104	0.0331
	Longevity	-0.083	0.081	0.3011	0.002	0.163	0.9888
	Rheumatoid arthritis	-0.0816	0.05	0.103	-0.093	0.123	0.4463
	Smoking status	0.113	0.05	0.0205	0.124	0.090	0.1657
	Type 2 diabetes	-0.145	0.07	0.0389	0.044	0.107	0.6837

Abbreviations: ADHD, attention-deficit hyperactivity disorder; BMI, body mass index; GPC, Genetics of Personality Consortium; GWAS, genome-wide association study; UKB, UK Biobank. Statistically significant *P*-values (after false discovery rate correction— $P < 0.0033$) are shown in bold.

single locus or biased the fit of the regression model, a 500-kb region centred on the *APOE* locus was removed and this phenotype was re-run. This additional model is referred to in Table 1 as 'Alzheimer's disease (500 kb)'.

Polygenic profiling. The UK Biobank genotyping data required recoding from numeric (1, 2) allele coding to standard ACGT format before being used in polygenic profile scoring analyses. This was achieved using a bespoke programme developed by one of the present authors (DCML), details of which are provided in the Supplementary Materials.

Polygenic profiles were created for 17 health-related phenotypes (Table 2 and Supplementary Table 2) in all genotyped participants using PRSice.⁴² This software calculates the sum of alleles associated with the phenotype of interest across many genetic loci, weighted by their effect sizes estimated from a GWAS of that phenotype in an independent sample. Before creating the scores, SNPs with a minor allele frequency < 0.01 were removed, and clumping was used to obtain SNPs in linkage equilibrium with an $r^2 < 0.25$ within a 200-bp window. Multiple scores were then created for each phenotype containing SNPs selected according to the significance of their association with the phenotype. The GWAS summary data for the 12 health-related phenotypes were used to create five polygenic profiles for each in the UK Biobank participants, at thresholds of $P < 0.01$, $P < 0.05$, $P < 0.1$, $P < 0.5$ and all SNPs. The most predictive threshold will be presented in the main tables of this paper. The full results, including all five thresholds, can be found in Supplementary Table 2.

Associations between the polygenic profiles and neuroticism were examined in linear regression models, adjusting for age at measurement, sex, genotyping batch and array, assessment centre and the first 10 genetic principal components to adjust for population stratification. We corrected for multiple testing across all polygenic profile scores at all significance thresholds for associations with neuroticism using the false discovery rate method.⁴³ As neuroticism on average is higher in females and likely declines with age,² age- (under and over 60 years old) and gender-stratified models were examined.

RESULTS

Within UK Biobank, 108 038 individuals with genotype data completed the Neuroticism scale of the EPQ-R Short Form. Their mean (s.d.) score for neuroticism was 4.02 (3.17).

The genetic correlation between neuroticism measured in the UK Biobank and neuroticism measured in the GPC is 1.0 (s.e. = 0.11).

Table 1 shows the genetic correlations obtained using LD score regression between neuroticism in UK Biobank and neuroticism

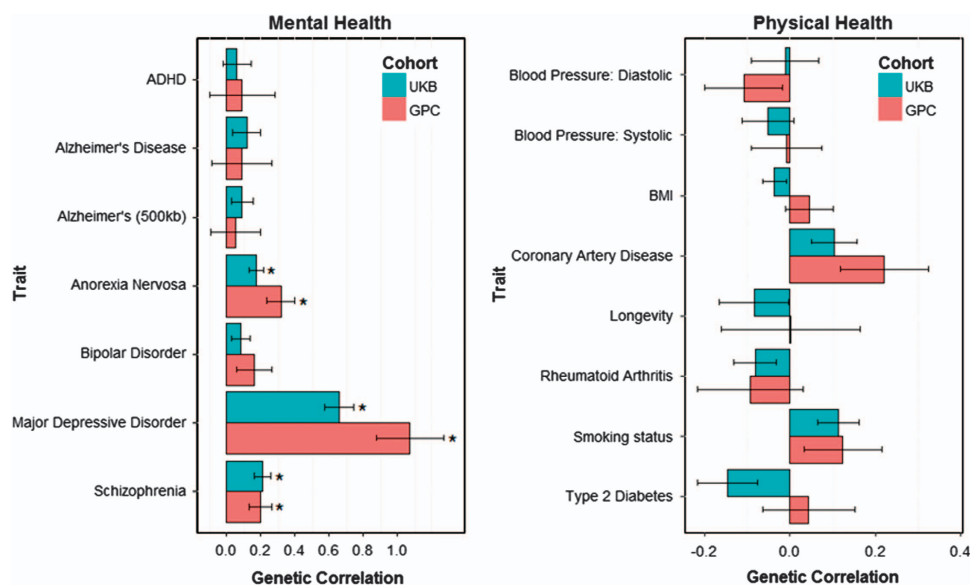
from the GPC, and the published GWAS results on the health-related traits. Neuroticism in UK Biobank showed significant positive genetic correlations with three traits, all related to mental health, namely major depressive disorder ($r_g = 0.66$), schizophrenia ($r_g = 0.21$) and anorexia nervosa ($r_g = 0.17$). The findings replicated when using Neuroticism from the GPC. There were no significant genetic correlations between neuroticism and either the other mental health-related traits (ADHD, Alzheimer's disease and bipolar disorder) or any of the physical health-related traits (systolic and diastolic blood pressure, BMI, coronary artery disease, type 2 diabetes, smoking status, rheumatoid arthritis or longevity). These results are shown graphically in Figure 1.

Table 2 shows the results of the polygenic risk scoring, using the most predictive threshold of the five that were created. Higher polygenic risk for six mental health-related traits, bipolar disorder, borderline personality, major depressive disorder, negative affect, neuroticism (calculated using summary data from the GPC) and schizophrenia, was significantly associated with higher levels of neuroticism in UK Biobank (standardised β between 0.017 and 0.043). There were no significant associations between neuroticism and polygenic risk for the other mental health-related traits examined, namely ADHD, Alzheimer's disease and anorexia nervosa. Polygenic risk scores for three physical health-related traits were significantly associated with neuroticism: higher polygenic risk for BMI was associated with lower levels of neuroticism ($\beta = -0.0095$, $P = 0.0015$), higher polygenic risk for coronary artery disease was associated with higher levels of neuroticism ($\beta = 0.011$, $P = 0.0003$) and higher polygenic profile scores for smoking were associated with higher levels of neuroticism ($\beta = 0.17$, $P = 2.48 \times 10^{-7}$). No significant associations were found between polygenic risk for the other physical health-related traits (systolic and diastolic blood pressure, type 2 diabetes, rheumatoid arthritis or longevity) and neuroticism. To test whether the false discovery rate significant association between polygenic risk for coronary artery disease and neuroticism was confounded by individuals diagnosed with cardiovascular disease, 2717 individuals who had had a heart attack and 2468 individuals with angina were removed from the regression analysis. Our estimate of the association between polygenic risk of coronary artery disease and neuroticism was unchanged by this exclusion. The same applied for major depressive disorder (excluding 7494 individuals with a probable diagnosis of major

Table 2. Associations between polygenic risk scores for mental and physical health-related traits created from GWAS consortia summary data and neuroticism in UK Biobank participants, adjusted for age, sex, assessment centre, genotyping batch and array, and 10 principal components for population stratification

Trait category	Traits from GWAS consortia	Neuroticism (n = 108 038)			
		Threshold	β	R ²	P
Mental health	ADHD	0.05	0.0045	2.06×10^{-5}	0.1292
	Alzheimer's disease	0.05	-0.0065	4.16×10^{-5}	0.0312
	Anorexia nervosa	0.1	0.0054	2.87×10^{-5}	0.0735
	Bipolar disorder	0.5	0.0171	0.0003	1.71×10^{-8}
	Borderline personality	1	0.0150	0.0002	5.43×10^{-7}
	Major depressive disorder	1	0.0357	0.0012	1.23×10^{-31}
	Negative affect (anxiety)	1	0.00949	8.99×10^{-5}	1.55×10^{-3}
	Neuroticism (GPC)	0.5	0.0433	0.0020	1.77×10^{-47}
	Schizophrenia	0.1	0.0359	0.0012	7.88×10^{-32}
Physical health	Blood pressure: diastolic	0.1	-0.0047	2.20×10^{-5}	0.1167
	Blood pressure: systolic	0.05	-0.0016	2.51×10^{-6}	0.5969
	BMI	0.01	-0.0095	9.00×10^{-5}	0.0015
	Coronary artery disease	0.1	0.0109	0.00012	0.0003
	Longevity	0.05	-0.0051	2.55×10^{-5}	0.0917
	Rheumatoid arthritis	0.5	-0.0007	5.09×10^{-5}	0.8266
	Smoking status	0.5	0.0167	0.0002	2.48×10^{-7}
	Type 2 diabetes	0.01	-0.0031	9.67×10^{-6}	0.2989

Abbreviations: ADHD, attention-deficit hyperactivity disorder; BMI, body mass index; GPC, Genetics of Personality Consortium; GWAS, genome-wide association study. The associations between the polygenic risk scores and neuroticism with the largest effect size (threshold) are presented. Statistically significant *P*-values (after false discovery rate correction— $P < 0.0065$) are shown in bold.

**Figure 1.** Barplot of genetic correlations (s.e.) calculated using linkage disequilibrium score regression between neuroticism in UK Biobank (UKB) and the Genetics of Personality Consortium (GPC), and mental and physical health measures from genome-wide association study consortia. * $P < 0.0033$. ADHD, attention-deficit hyperactivity disorder; BMI, body mass index.

depression or bipolar disorder⁴⁴), where the estimate of the association showed little change. The complete polygenic risk score results, including all five thresholds, are shown in Supplementary Table 2.

Age- and gender-stratified analyses indicated there were no substantial differences by age or gender for 13 out of 17 traits. Four traits did show a potential age or gender effect. Polygenic risk for anorexia nervosa predicts neuroticism in males, but not in females. Polygenic risk for diastolic blood pressure predicts neuroticism only in females over 60 years of age. The strongest

associations between polygenic risk for negative affect and smoking status, and neuroticism, are in females under 60 years of age. The full results for these stratified analyses can be found in Supplementary Table 3.

DISCUSSION

In this study of 108 038 men and women from UK Biobank who had been genotyped and assessed for neuroticism, we exploited the summary results of 17 large international GWAS consortia to

examine whether there is pleiotropy between neuroticism and a range of physical and mental health outcomes using two methods, LD score regression and polygenic profile scoring. Summary results from two separate GWASs of neuroticism showed a genetic correlation of 1.0. Using summary data from both of these studies of neuroticism, the genetic correlations that were calculated with physical and mental health were very similar. As regards the six mental health outcomes that were investigated using both LD score regression and polygenic profile scoring, we found consistent evidence of pleiotropy between neuroticism and both major depression and schizophrenia with these methods, showing that, to a significant degree, the same genetic variants are responsible for the heritability of each pair of phenotypes and that genetic variants associated with major depression or schizophrenia in GWAS consortia are significantly predictive of variation in neuroticism in UK Biobank. There was some evidence for pleiotropy between neuroticism, and bipolar disorder, borderline personality, anorexia nervosa and negative affect on the basis of results from polygenic profile scoring or LD score regression, respectively, but the extent of these associations varied according to the method used. In all cases where there was a significant finding using one method but not the other, the direction of effect was the same using both methods. We found no evidence of pleiotropy between neuroticism and the other mental health outcomes examined—ADHD and Alzheimer's disease. Of the eight physical health outcomes studied, none showed evidence of pleiotropy with neuroticism on the basis of the genetic correlations obtained from LD score regression, but there was some indication of genetic overlap between neuroticism and coronary artery disease, smoking status and BMI. Higher polygenic risk for coronary artery disease and smoking status was significantly associated with higher levels of neuroticism, and polygenic risk for higher BMI was associated with lower levels of neuroticism. No associations were found between polygenic risk for the other physical health-related traits (systolic and diastolic blood pressure, rheumatoid arthritis, type 2 diabetes or longevity) and neuroticism.

Previous investigations into pleiotropy between neuroticism and mental health outcomes using polygenic risk profiling have found evidence of substantial shared genetic aetiology between neuroticism and major depression.^{31,45,46} Our observations in the present, much larger, sample confirm those findings and for, we believe, the first time quantify the extent to which the same genetic variants are responsible for the heritability in these two phenotypes, using an additional metric, LD score regression.³² The relatively high genetic correlation between neuroticism and major depression ($r_g=0.66$), identified in our study, is similar to the genetic correlation identified in a previous twin study ($r_g=0.43$).³⁰ Our results also provide the first evidence, to our knowledge, that the phenotypic correlations found between neuroticism and schizophrenia^{47,48} are due at least in part to genetic overlap. The extent of pleiotropy between anorexia nervosa or bipolar disorder and neuroticism has been unclear, though there is some, though limited, evidence to link both disorders phenotypically with neuroticism.^{5,49} A previous study found no significant association between polygenic risk scores for neuroticism and bipolar disorder, but the sample size was small.⁴⁶ In this much larger sample, higher polygenic risk scores for bipolar disorder were significantly predictive of higher neuroticism, but results of LD score regression showed little indication of genetic correlation between neuroticism and this disorder. We found a small but highly significant genetic correlation between neuroticism and anorexia ($r_g=0.17$), but there was no association between polygenic risk scores for this condition and neuroticism. Although there is now considerable evidence that neuroticism is a risk factor for the development of Alzheimer's disease,⁹ there was no indication in our analyses that shared genes account for this link.

So far as we are aware, there have been no previous investigations of the extent of pleiotropy between neuroticism and physical health outcomes. This may be because, whereas there is considerable evidence for phenotypic associations between higher neuroticism and poorer self-rated health or greater somatic complaints,^{13–18} fewer studies have examined neuroticism as a predictor of objectively measured physical health outcomes, and findings on such outcomes as coronary heart disease, blood pressure, BMI and all-cause mortality have been inconsistent.^{19–26} Of the eight objectively measured physical health outcomes included in the current study, three showed evidence of a degree of genetic pleiotropy with neuroticism: coronary artery disease, smoking status and BMI. Neither demonstrated any measurable genetic correlation with neuroticism, but higher polygenic risk score for coronary artery disease was associated with higher neuroticism. This is consistent with the finding in pooled data from three cohorts that higher neuroticism was associated with increased mortality from coronary heart disease.²⁰ Higher polygenic risk for BMI was associated with lower neuroticism. The direction of this association was unexpected. Findings on the phenotypic relationships between neuroticism and BMI have produced inconsistent results: one study showed higher neuroticism was associated with higher BMI,²² but another found no association.²⁵

The chief strength of our study is the large sample size that permits powerful, robust tests of genetic association. Second, all the UK Biobank genetic data were processed at the same location and on the same platform. Finally, use of summary data from 17 large international GWAS consortia studies allowed us to perform a comprehensive examination of the degree of pleiotropy between neuroticism and a range of physical and mental health-related phenotypes, and to produce many of the first estimates of the genetic correlation between neuroticism and these phenotypes.

Our study also has some limitations. First, the GWAS studies we curated to carry out LD score regression and extract polygenic risk scores often involved meta-analyses of results from data sets with considerable heterogeneity in sample size, genome-wide imputation quality and measurement of phenotypes. With larger and more consistent independent data sets, it should be possible to use the polygenic risk scores to predict more variance in neuroticism. Second, we restricted the genotyped samples to individuals of white British ancestry in order to minimise any influence of population structure. Our results therefore need to be replicated in large samples with different genetic backgrounds as we did not have the power to model data from UK Biobank individuals of other ancestries. In the stratified analysis 13 out of 17 traits did not indicate a gender or age effect. These stratified results need to be interpreted with caution; they were mostly null, and no multiple testing correction was applied due to the high correlations between the different models. The four traits that did indicate potential gender or age effects need to be replicated in an independent sample, before any conclusions can be drawn from them.

We note that genetic correlations reflect the amount of the genetic influence on two traits that is common to both. This is independent of the heritability of either trait. Therefore, it is entirely possible for a trait to have a small proportion of variance accounted for by genetic variants, but to have a high genetic correlation with another trait. The amount of variance explained by each polygenic profile score is small, as would be expected by the fact that not all SNPs were genotyped, and those that were do not necessarily accurately tag the causal genetic variants. The polygenic risk score most predictive threshold varied between health traits, suggesting that the amount of shared genetic aetiology between neuroticism and each of the health traits differs. Although testing multiple thresholds may be deemed to increase the multiple testing problem, it should be noted that the

SNPs included in each threshold are not independent. Also, at least for major depressive disorder and schizophrenia, pleiotropy was quantified using LD score regression, which involved only a single test per pair of phenotypes. The estimate of neuroticism variance explained by each polygenic profile should be considered as the minimum estimate of the variance explained. Owing to pruning SNPs in LD, the polygenic risk score method makes the assumption of a single causal variant being tagged in each LD block considered. If this assumption is not true for the phenotypes considered, the proportion of variance explained will be underestimated here.

In this large sample from UK Biobank, we aimed to discover whether shared genetic aetiology explained part of the associations between neuroticism and various physical and mental health outcomes. Our findings suggest that associations between neuroticism and several mental health outcomes including major depression, schizophrenia, bipolar disorder and anorexia nervosa are in part due to shared genetic influences. We found that polygenic risk scores for coronary artery disease, smoking and BMI were predictive of neuroticism scores. This large-scale mapping of the extent of pleiotropy between neuroticism and physical and mental health outcomes adds to our understanding of the cause of links between this important personality trait and later health.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (<http://www.nature.com/tp>)

6.3. Conclusion

As discussed by Gale et al. (2016) in Section 6.2, neuroticism was genetically associated with multiple mental health traits. Significant genetic correlations identified between neuroticism and anorexia nervosa, major depressive disorder and schizophrenia in UK Biobank were replicated using neuroticism summary statistics from the Genetics of Personality Consortium. Some evidence was found for a shared genetic aetiology between neuroticism and physical health using PRS analysis; however, LDSR did not find any association between neuroticism and the physical health variables studied here. Overall, these results aid to a better understanding of the relationship between neuroticism and health. This Chapter examined the associations between one measure of negative emotions, i.e. neuroticism, and health; the next Chapter will examine the associations between self-reported tiredness, as a measure related to negative emotions, and health.

7. Genetic contributions to self-reported tiredness

7.1. Introduction

Fatigue is common in the general population and has been linked to higher levels of neuroticism and psychological distress, but also to poorer physical health. Both behavioural and molecular genetic studies have indicated genetic contributions to fatigue (Schlauch et al., 2016; Schur, Afari, Goldberg, Buchwald, & Sullivan, 2007) and behavioural genetic studies suggested that the associations between neuroticism and fatigue could be due to a shared genetic aetiology (Charles et al., 2008; Kato et al., 2006). The molecular genetic studies examining the genetic contributions to people's differences in fatigue are limited by the small sample sizes. This Chapter will examine the genetic contributions to fatigue, measured by self-reported tiredness in the large UK Biobank sample, and will also examine the shared genetic aetiology between self-reported tiredness and physical and mental health. This study has been published in *Molecular Psychiatry* and is included in full in Section 7.2.

7.2. Genetic contributions to self-reported tiredness

ORIGINAL ARTICLE

Genetic contributions to self-reported tiredness

V Deary^{1,7}, SP Hagenaars^{2,3,4,7}, SE Harris^{2,5}, WD Hill^{2,3}, G Davies^{2,3}, DCM Liewald^{1,2}, International Consortium for Blood Pressure GWAS, CHARGE Consortium Aging and Longevity Group, CHARGE Consortium Inflammation Group, AM McIntosh⁴, CR Gale^{2,3,6,7} and IJ Deary^{2,3,7}

Self-reported tiredness and low energy, often called fatigue, are associated with poorer physical and mental health. Twin studies have indicated that this has a heritability between 6 and 50%. In the UK Biobank sample ($N = 108\,976$), we carried out a genome-wide association study (GWAS) of responses to the question, 'Over the last two weeks, how often have you felt tired or had little energy?' Univariate GCTA-GREML found that the proportion of variance explained by all common single-nucleotide polymorphisms for this tiredness question was 8.4% (s.e. = 0.6%). GWAS identified one genome-wide significant hit (Affymetrix id 1:64178756_C_T; $P = 1.36 \times 10^{-11}$). Linkage disequilibrium score regression and polygenic profile score analyses were used to test for shared genetic aetiology between tiredness and up to 29 physical and mental health traits from GWAS consortia. Significant genetic correlations were identified between tiredness and body mass index (BMI), C-reactive protein, high-density lipoprotein (HDL) cholesterol, forced expiratory volume, grip strength, HbA1c, longevity, obesity, self-rated health, smoking status, triglycerides, type 2 diabetes, waist-hip ratio, attention deficit hyperactivity disorder, bipolar disorder, major depressive disorder, neuroticism, schizophrenia and verbal-numerical reasoning (absolute r_g effect sizes between 0.02 and 0.78). Significant associations were identified between tiredness phenotypic scores and polygenic profile scores for BMI, HDL cholesterol, low-density lipoprotein cholesterol, coronary artery disease, C-reactive protein, HbA1c, height, obesity, smoking status, triglycerides, type 2 diabetes, waist-hip ratio, childhood cognitive ability, neuroticism, bipolar disorder, major depressive disorder and schizophrenia (standardised β 's had absolute values < 0.03). These results suggest that tiredness is a partly heritable, heterogeneous and complex phenomenon that is phenotypically and genetically associated with affective, cognitive, personality and physiological processes.

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INTRODUCTION

'Hech, sirs! But I'm wabbit, I'm back frae the toon; I ha'ena dune pechin'—jist let me sit doon.'

From *Glesca*' by William Dixon Cocker (1882–1970)

The present study examines genetic contributions to how the UK Biobank's participants answered the question, 'Over the last two weeks, how often have you felt tired or had little energy?' Ideal questionnaire items do not have conjunctions, but the 'or' is understandable here, and it may even allow capture of both peripheral and central fatigue. The first and last authors of the present study grew up in South Lanarkshire in Scotland, where fatigue was often self-reported in terms of feeling 'wabbit'. The Scots word wabbit encompasses both peripheral fatigue, the muscle weakness after a long walk, and central fatigue, the reduced ability to initiate and/or sustain mental and physical activity, such as we might experience while having flu. Throughout the paper, we refer mainly to the single English words 'fatigue' and/or 'tiredness' as the construct captured by the question, but the Scottish vernacular word is a good reminder of the subjective 'feel' of fatigue.

Fatigue is a common complaint. In a Dutch adult, general population survey with 9375 respondents, 4.9% reported short-term fatigue (< 6 months duration), 30.5% chronic fatigue (> 6 months duration) and 1% fulfilled diagnostic criteria for chronic fatigue syndrome (CFS).¹ These findings are similar to a London-based survey of general practice patients in England, aged 18–45 years, with 15 283 respondents, where 36.7% reported substantial fatigue, 18.3% substantial fatigue of > 6 months duration and 1% fulfilled the diagnostic criteria for CFS.² Two other large surveys of US workers and community-dwelling adults aged 51 years and over report fatigue rates of 37.9% (2-week period prevalence) and 31.2% (1-week period prevalence) respectively.^{3,4} In an early review of fatigue epidemiology, Lewis and Wessely⁵ argue that fatigue 'is best viewed on a continuum', and the continuous distribution of fatigue in the general population is supported by the Pawlikowska *et al.*² study. Fatigue is also a common presentation in primary care. In a survey of 1428 consultations to 89 general practitioners in Ireland, fatigue prevalence was 25% and the main reason for attendance in 6.5%.⁶

Demographically, higher levels of self-reported fatigue are associated with female sex, lower socioeconomic status¹ and poorer self-rated health status.⁷ There are less clear associations

¹Department of Psychology, Northumbria University, Newcastle, UK; ²Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK; ³Department of Psychology, University of Edinburgh, Edinburgh, UK; ⁴Division of Psychiatry, University of Edinburgh, Edinburgh, UK; ⁵Medical Genetics Section, University of Edinburgh, Centre for Genomic and Experimental Medicine and MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK and ⁶MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK. Correspondence: Dr V Deary, Department of Psychology, Northumbria University, Newcastle NE1 8ST, UK.

E-mail: vincent.deary@northumbria.ac.uk

or Professor IJ Deary, Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK.

E-mail: i.deary@ed.ac.uk

⁷These authors contributed equally to the work.

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between age and fatigue, with some studies reporting a small but significant positive correlation between age and fatigue,² whereas others report no association⁶ or a negative association.^{1,7} There is a clearer link with the Fried phenotype of frailty in older adults,⁸ which has significant associations with mortality. The frailty phenotype comprises weakness (as measured by grip strength), weight loss, reduced mobility, reduced walking speed and fatigue.⁹

Fatigue is associated with a number of lifestyle-related factors and conditions. Smoking is a risk factor for fatigue¹⁰ and fatigue has strong cross-sectional associations with type 2 diabetes¹¹ and increased body mass index (BMI).¹² Fatigue is consistently associated with poorer physical and mental health status. It is one of the most common symptom complaints of cancer patients. For those undergoing treatment, prevalence estimates vary between 25 and 99%, and 25 and 30% of survivors report long-term fatigue.¹³ Fatigue is also a significant symptom of, to name just a few conditions, primary biliary cirrhosis,¹⁴ multiple sclerosis,¹⁵ rheumatoid arthritis,¹⁶ primary Sjogren's syndrome¹⁷ and Parkinson's disease.¹⁸ It is associated with chronic disease in general, and there is a linear relationship between number of chronic diseases and self-reported fatigue.¹⁹ Fatigue is also associated with depression,²⁰ with self-reported psychological distress,^{2,21} and with the personality trait of neuroticism.^{22,23}

Research into the biological mechanisms of fatigue has focussed on a few key areas. Fatigue is associated with the cytokine-mediated inflammatory response, particularly interleukin-1beta and interleukin-6. These latter have been shown, for instance, to be elevated in cancer patients,²⁴ and administration of interferon-alpha produces depression and/or fatigue in the majority of patients receiving it as a treatment.²⁵ Hypothalamic-pituitary-adrenal axis dysregulation in the form of hypocortisolaemia, blunted diurnal variation and blunted stress reactivity have been found in the cross-sectional studies of CFS patients (see Tomas *et al.*²⁶ for a recent review). Other popular candidate aetiological mechanisms for fatigue include serotonin pathways, circadian dysregulation, autonomic dysfunction,¹⁷ 5HT neurotransmitter dysregulation, alterations in ATP metabolism and vagal afferent activation.²⁴ Some authors have suggested that, rather than being located with one biological system, fatigue represents a systemic dysregulation of the interaction between these systems.²⁷

At the other end of the biopsychosocial spectrum, psychosocial models of fatigue focus on the role that the individual's response to their symptom may serve in perpetuating it. For instance, in a cross-sectional study of 149 patients with multiple sclerosis, illness-related cognitions and behaviours were associated with a higher level of fatigue independent of neurological impairment.²⁸ More integrative models are predicated on the notion of allostatic load, the psychophysiological work done to adjust to stress and its impact upon the body's self-regulatory systems. As such, these models complement biological accounts of fatigue and provide potential pathways for integrating psychosocial and biological findings.²⁹ Multifactorial accounts and models of fatigue exist in multiple sclerosis,³⁰ primary biliary cirrhosis,¹⁴ obesity,³¹ diabetes,³² frailty³³ and cancer.¹³ These multifactorial models postulate that fatigue is likely to be the product of physiological factors (generic, such as inflammation and/or disease specific such as hyperglycaemia in diabetes), psychosocial factors (for example, emotional distress), lifestyle and behavioural factors (for example, reduced activity), illness consequences (for example, sleep disturbance and weakness) and the interaction of these contributors.

Research into the genetics and epigenetics of fatigue has tended to focus on genes associated with the biological mechanisms described above, and done so usually within fatiguing illnesses such as those listed above. Candidate gene studies have suggested several genes to be involved in CFS, particularly genes involved in the immune system and

Hypothalamic-pituitary-adrenal axis. Reviewing this literature, Landmark-Høyvik *et al.*³⁴ suggest that findings are inconclusive, and are hampered by phenotypic heterogeneity, lack of power and poor study design. For example, the candidate gene studies included in the Landmark-Høyvik paper had sample sizes between 2 and 248 individuals, and the results have not been replicated. Twin studies have shown the heritability of fatigue to be between 6 and 50% with a higher concordance in monozygotic twins than dizygotic twins.^{35,36} One of these studies³⁶ did not show any sex-specific patterns of genetic influences in a Swedish sample, whereas the other one³⁵ showed differences in the amount of variance explained by the genetic effect for males and females. Around half the variance in males was explained by the genetic effects compared to only a fifth of the variance in females. In a study of fatigue, insomnia and depression in 3758 twins (893 monozygotic pairs and 884 dizygotic pairs), the best model was a common pathway model, suggesting that the high association between the symptoms (correlations of 0.35–0.44) was mediated by an underlying common factor whose variation was 49% genetic and 51% unique environmental.³⁷ This study showed that unique specific variance in fatigue was 38% genetic and 62% unique environmental, which supports a previous study, suggesting that fatigue is largely attributable to additive genetic factors.³⁸ Genome-wide association studies (GWAS) have shown an association between single-nucleotide polymorphisms (SNPs) in genes associated with impaired cognitive abilities (*GRIK2*, $P=1.26 \times 10^{-11}$)^{39,40} and the circadian clock (*NPAS2*, not genome-wide significant)⁴⁰ and CFS, but this was in a sample of just 42 cases of CFS and 38 controls, lacking statistical power to detect genome-wide findings.

To sum up in the words of Landmark-Høyvik *et al.*:⁴¹ 'fatigue can be conceptualised as a final common end point for psychological and biological processes. Fatigue is therefore both heterogeneous (occurring across different conditions) and multifactorial'. Given that, it could be argued that it is futile to search for a shared genetic contribution to tiredness, as it may not exist. However, in line with other fatigue research programmes⁴² and the research cited above, we judge that the best way to approach this complexity is to conduct large, well-designed studies focussing on specific areas of the biopsychosocial spectrum, and that to date no large study has done this at the genetic level.

Tiredness can be the result of external factors—such as poor sleep—or inherent factors—such as personality traits or poor health. It is therefore important that we clarify the scope of the present study in terms of what questions we can ask, and how definitively we can answer them. By averaging tiredness across a large sample and performing a GWAS, the present study will primarily pick upon the genetic links between tiredness and inherent factors. These are likely to be various, so we will seek to bring some clarity to what we consider to be the likely genetic heterogeneity of tiredness by posing the following questions:

1. Is there a direct genetic contribution to self-reported tiredness *per se*, not accounted for the factors in questions 2–4 below?
2. Is tiredness genetically linked to proneness to health-related traits?
3. Is tiredness genetically linked to a systemic proneness to poor health?
4. Is there a genetic relationship between the personality trait of neuroticism and tiredness?

With regard to questions 2 and 3, it is important to remember that a positive answer may constitute more than the obvious conclusion that the presence of an illness phenotype is inevitably accompanied by tiredness. Our analyses of UK Biobank data capture genetic predisposition to illness rather than its actual presence; we will address this in our polygenic prediction sensitivity analysis.

The aim of the present study, then, is to understand further the genetic contribution to self-reported tiredness and/or low energy. We conducted a genome-wide association analysis, in the UK Biobank sample, of a response to a single item question: 'Over the past two weeks, how often have you felt tired or had little energy?' On the basis of the foregoing literature overview, we also investigated pleiotropy with physical- and mental health-related traits, and we specifically investigated pleiotropy with factors associated with allostatic load as a first step towards answering question three above. The current study design, using > 100 000 UK Biobank participants, directly addresses the main limitation from the previous studies by substantially increasing the sample size. In addition, we complement this with SNP-based heritability estimates of tiredness, sex- and age-stratified analysis, and an examination of the genetic overlap of tiredness with many health-related traits.

MATERIALS AND METHODS

Study design and participants

UK Biobank is a large resource for identifying determinants of human diseases in middle-aged and older individuals (<http://www.ukbiobank.ac.uk>).⁴³ A total of 502 655 community-dwelling individuals aged between 37 and 73 years were recruited in the United Kingdom between 2006 and 2010. Baseline assessment included cognitive testing, personality self-report, and physical and mental health measures. For the present study, genome-wide genotyping data were available for 112 151 participants (58 914 females and 53 237 males) after quality control (see below). They were aged from 40 to 73 years (mean = 56.9 years, s.d. = 7.9). UK Biobank received ethical approval from the Research Ethics Committee (REC reference for UK Biobank is 11/NW/0382). This study has been completed under UK Biobank application 10279. Figure 1 shows the study flow for the present report.

Procedures

Tiredness. Participants were asked the question, 'Over the past two weeks, how often have you felt tired or had little energy?' Possible answers were: 'Not at all/Several days/More than half the days/Nearly every day/Do not know/Prefer not to answer'. This question was asked as part of the Mental Health Questionnaire, which consists of items from the Patient Health Questionnaire.⁴⁴ Participants answering with 'Do not know' or 'Prefer not to answer' were excluded, resulting in a four-category variable for tiredness ranging from 'Not at all' to 'Nearly every day'. We will refer to

this question in the rest of the paper as 'tiredness', but we ask the reader to bear in mind the question as it was asked, that is, its referring to tiredness and/or low energy.

Genotyping and quality control. The interim release of UK Biobank included genotype data for 152 729 individuals, of whom 49 979 were genotyped using the UK BiLEVE array and 102 750 using the UK Biobank axiom array. These arrays have over 95% content in common. Details of the array design, genotyping procedures and quality control details have been published elsewhere.^{45,46}

Imputation. An imputed data set was made available as part of the UK Biobank interim data release. The 1000 Genomes phase 3 and UK10K haplotype reference panels were merged and the genotype data imputed to this merged reference panel. Further details can be found at the following URL: <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020>. Autosomal variants with a minor allele frequency $\leq 0.1\%$ and an imputation quality score of < 0.1 were excluded from further analysis ($N \sim 17.3M$ SNPs).

Curation of summary results from GWAS consortia on health-related variables. Published summary results from international GWAS consortia were gathered to derive genetic correlations using the linkage disequilibrium (LD) score regression method and perform polygenic profile score analysis between the UK Biobank tiredness variable and the genetic predisposition to multiple health-related traits. Details of the health-related variables, the consortia's websites, key references for each consortium and number of subjects included in each consortium's GWAS are given in Supplementary Table 1.

Statistical analysis

Phenotypic correlations. Spearman's rank correlation coefficients were calculated between responses to the tiredness question, grip strength, forced expiratory volume in 1 s, height, BMI, self-rated health, verbal-numerical reasoning and neuroticism, all of which were measured phenotypes in UK Biobank. Details on measurements of these phenotypes can be found in the Supplementary Material.

Genetic association analysis. A total of 111 749 individuals answered the tiredness question and had genotypic information. After visual inspection of the distribution of the UK Biobank tiredness variable no exclusions were made. Prior to analysis, tiredness was adjusted for age, sex, assessment centre, genotyping batch and array, and 10 principal components for population stratification. Genotype-phenotype association analyses were conducted using SNPTTEST v2.5.1 (ref. 47) and can be found at the following URL: https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html#introduction. An additive model was specified using the 'frequentist 1' option. Genotype uncertainty was accounted for by analysing genotype dosages.

Genetic association analyses were also performed on the following UK Biobank phenotypes to perform further analyses: self-rated health,⁴⁸ grip strength, forced expiratory volume in 1 s, neuroticism,⁴⁹ verbal-numerical reasoning.⁵⁰ We specifically examined whether any variants associated with tiredness were also associated with grip strength, self-rated health and neuroticism because we judged these to provide some coverage of physical and mental resilience in UK Biobank.

Estimation of SNP-based heritability. To estimate the proportion of variance explained by all common SNPs in tiredness, univariate GCTA-GREML analysis was performed.⁵¹ This analysis included only unrelated individuals, using a relatedness cutoff of 0.025 in the generation of the genetic relationship matrix.

Gene-based association analysis. Gene-based associations were derived using MAGMA,⁵² using the summary GWAS statistics for tiredness. SNPs were assigned to 18 062 genes using the National Center for Biotechnology Information build 37.3. The gene boundary was defined as the start and stop site of each gene. To account for LD between the SNPs used, the European panel of the 1000 Genomes data (phase 1, release 3) was used. A Bonferroni correction was used to control for 18 062 tests ($\alpha = 0.05/18\,062$; $P < 2.768 \times 10^{-6}$).

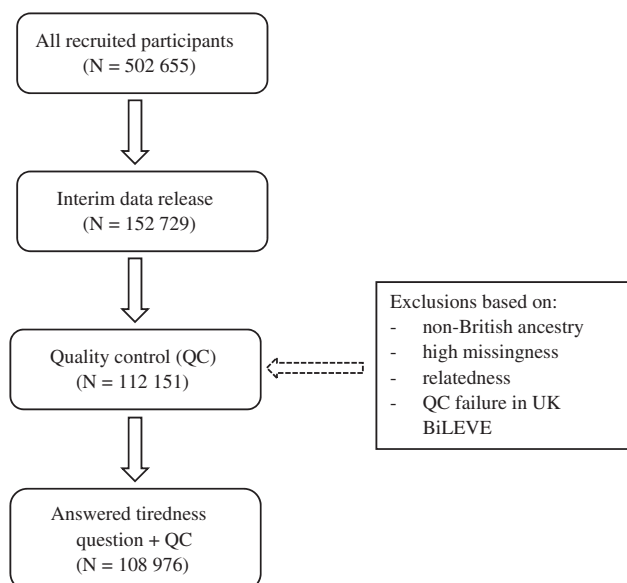


Figure 1. Flow diagram of participant selection.

Partitioned heritability. The summary statistics from the GWAS on tiredness was partitioned into functional categories using the same data processing pipeline as Finucane *et al.*⁵³ more details on this method can be found in the Supplementary Materials.

Shared genetic aetiology: LD score regression and polygenic profiling. Genetic associations between tiredness and health-related variables from GWAS consortia were computed using two methods, LD score regression and polygenic profile score analysis. Each provides a different metric to infer the existence of loci contributing to pairs of traits. LD score regression was used to derive genetic correlations between two traits; this tests the degree to which the polygenic architecture of one trait overlaps with that of other traits. Polygenic profile score analysis was used to test the extent to which individual differences in the tiredness phenotype in UK Biobank could be predicted by polygenic profile scores predictive of the health-related traits from other GWAS consortia. Both of these methods are dependent each on trait being polygenic in nature, that is, where a large number of variants of small effect contribute towards phenotypic variation.^{54,55} Bivariate LD score regression was performed between tiredness and 29 health-related traits. Polygenic profile score analysis was performed on 26 of the 29 health-related traits, as this method requires independent samples to provide the summary GWAS information from which the polygenic profile score is computed.

Bivariate LD score regression: This was used to quantify the extent of genetic overlap between tiredness in UK Biobank and 29 health-related traits.^{55,56} This technique examines the correlational structure of the SNPs found across the genome. In the present study, LD score regression was used to derive genetic correlations between tiredness and health-related traits using the GWAS results of 25 large GWAS consortia and four UK Biobank phenotypes. The data processing pipeline devised by Bulik-Sullivan *et al.*⁵⁵ was followed. To ensure that the genetic correlation for the Alzheimer's disease phenotype was not driven by a single locus or biased the fit of the regression model, a 500-kb region centred on the APOE locus was removed and this phenotype was re-run. This additional model is referred to in the tables and figures as 'Alzheimer's disease (500 kb)'.

Polygenic profile scores: The UK Biobank genotyping data were recoded from numeric (1,2) allele coding to standard ACGT coding using a bespoke programme developed by one of the present authors (DCML).⁴⁶ Polygenic profile scores were created for 25 health-related traits in all genotyped participants using PRSice.⁵⁷ Prior to creating the scores, SNPs with a minor allele frequency <0.01 were removed and clumping was used to obtain SNPs in linkage equilibrium with an $r^2 < 0.25$ within a 200 bp window. Five polygenic profile scores were created for each trait including SNPs according to their significance of association with the relevant trait at P -value thresholds of $P < 0.01$, $P < 0.05$, $P < 0.1$, $P < 0.5$, and all SNPs.

Regression models were used to examine the association between the polygenic profile scores and tiredness in UK Biobank, adjusting for age at measurement, sex, genotyping batch and array, assessment centre, and the first 10 principal components for population stratification. All associations were corrected for multiple testing using the false discovery rate (FDR) method.⁵⁸ Sensitivity analyses were performed to test whether the results were confounded by individual's neuroticism levels, their self-rated health scores or a diagnosis of major depressive disorder. This was done by adjusting the models for the neuroticism and self-rated health scores. Individuals with a probable diagnosis of major depressive disorder were excluded from the sensitivity analysis, based on the diagnostic method formulated by Smith *et al.*⁵⁹ Further details can be found in the Supplementary Material. To examine whether any association between polygenic profile score for type 2 diabetes and tiredness was confounded by having had a diagnosis of type 2 diabetes, all individuals with a self-reported doctor's diagnosis of type 2 diabetes were excluded from that specific sensitivity analysis (Supplementary Material). Multivariate regression was performed using all FDR significant polygenic profile scores and earlier described covariates.

Comparison of gene-based analysis results within UK Biobank. Gene-based associations for tiredness were compared with gene-based results for other UK Biobank health-related traits that, in the present report's results, showed a statistically significant genetic correlation with tiredness, using previously described methods.⁵²

Age- and sex-stratified analysis. On the basis of the age and sex distribution for tiredness (Supplementary Figure 1), further analyses examining

potential age and sex effects were performed. The sample was split by sex, as well as the following three age groups for each sex: 40 to < 50 years, 50 to < 60 years and 60 to < 70 years, one male aged > 70 years was excluded from these analyses. The analysis included heritability estimates for the eight different groups, genome-wide association analysis, and genetic correlations with BMI and waist-hip ratio, as these summary data were available separately for males and females. All models were adjusted for age (sex-stratified analyses), sex (age-stratified analysis) and the previously mentioned covariates (assessment centre, genotyping batch and array, and 10 principal components for population stratification).

Code availability. The code used to run the analysis is available from the authors upon request.

RESULTS

Phenotypic correlations

A total of 108 976 individuals from UK Biobank with genotypic data answered the question 'Over the past two weeks, how often have you felt tired or had little energy?', referred to hereinafter as 'tiredness'. There were 51 416 individuals who answered 'not at all', 44 208 individuals responded 'several days', 6404 individuals answered 'more than half the days' and 6948 individuals responded 'nearly every day'. Correlations indicated that individuals who reported feeling more tired tended to have lower grip strength, lower lung function, poorer self-rated health, lower scores for verbal-numerical reasoning and shorter stature (Table 1). Correlations indicated that individuals who reported feeling more tired tended to have a higher BMI and higher neuroticism scores (Table 1). Absolute effect sizes ranged from very small to moderate (Supplementary Figures 2a–f). The mean scores and distribution for each of these variables at each level of tiredness are shown in Supplementary Figure 2 and Supplementary Table 2.

Genome-wide association study

There was one genome-wide significant SNP (Affymetrix id 1:64178756_C_T; $P = 1.36 \times 10^{-11}$) on chromosome 1 (Figure 2). This SNP is not in a gene and does not have an rs id. It has both a low minor allele frequency (0.001) and a low imputation quality score (0.43). It is not in a peak with other SNPs. Therefore, this result should be treated with caution. Two suggestive peaks were identified on chromosomes 1 and 17, with the lowest P -values of 5.88×10^{-8} (rs142592148; an intronic SNP in *SLC44A5*) and 6.86×10^{-8} (rs7219015; an intronic SNP in *PAFAH1B1*) for each peak, respectively. The peak on chromosome 1 contains three genes (*CRYZ*, *TYW3* and *SLC44A5*). The peak on chromosome 17 contains one gene (*PAFAH1B1*). The *CRYZ*/*TYW3* locus has previously been associated with circulating resistin levels, a hormone associated with insulin resistance, inflammation, and risk of type 2 diabetes and cardiovascular disease.⁶⁰ *SLC44A5* encodes a solute carrier protein and is important for metabolism of lipids and

Table 1. Spearman phenotypic correlations between tiredness (responses to the question, 'Over the past two weeks, how often have you felt tired or had little energy?') and physical and mental health

	Tiredness
Self-rated health (N = 108 648)	–0.35
Grip strength (N = 108 573)	–0.12
Forced expiratory function in 1 s (N = 101 823)	–0.08
Height (N = 108 796)	–0.09
BMI (N = 108 681)	0.10
Verbal-numerical reasoning (N = 35 101)	–0.04
Neuroticism (N = 105 456)	0.39

Abbreviation: BMI, body mass index. All correlations had $P < 0.001$.

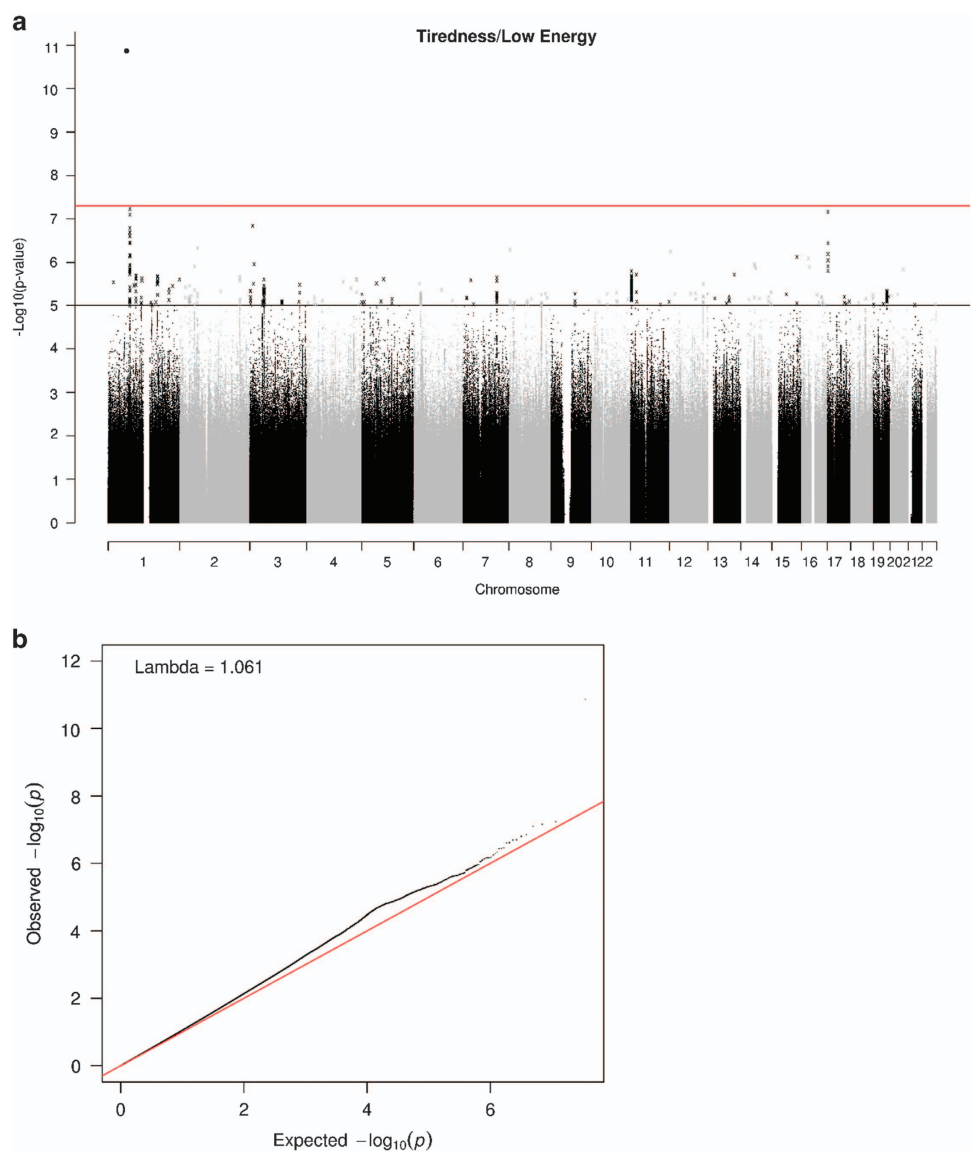


Figure 2. (a) Manhattan and (b) Q-Q plot of P -values of the SNP-based association analysis of tiredness (responses to the question, ‘Over the past two weeks, how often have you felt tired or had little energy?’). The red line on the Manhattan plot indicates the threshold for genome-wide significance ($P < 5 \times 10^{-8}$); the grey line on the Manhattan plot indicates the threshold for suggestive significance ($P < 1 \times 10^{-5}$). SNP, single-nucleotide polymorphism.

lipoproteins, and has been associated with birth weight in cattle.⁶¹ *PAFAH1B1* encodes a subunit of an enzyme that has important roles in brain development and spermatogenesis. Mutations in this gene cause the neurological disorder lissencephaly.⁶²

SNP-based heritability estimate

Using GCTA-GREML common SNPs were found to explain 8.4% (s.e. 0.6%) of the phenotypic variation of tiredness as measured in UK Biobank.

Gene-based association analysis

Gene-based association analysis identified five genes, *DRD2*, *PRRC2C*, *C3orf84*, *ANO10* and *ASXL3*, that attained genome-wide

Table 2. The genome-wide significant genes from the UK Biobank tiredness phenotype and the significance values for the same genes using the neuroticism, SRH and grip phenotypes, also in the UK Biobank sample					
CHR	Gene	Tiredness P	SRH P	Grip P	Neuroticism P
11	<i>DRD2</i>	2.94×10^{-7}	0.012	0.156	9.69×10^{-9}
1	<i>PRRC2C</i>	1.43×10^{-6}	0.002	0.314	0.020
3	<i>C3orf84</i>	1.45×10^{-6}	7.38×10^{-5}	0.001	0.016
3	<i>ANO10</i>	1.52×10^{-6}	0.058	0.728	0.001
18	<i>ASXL3</i>	2.67×10^{-6}	1.03×10^{-6}	0.052	1.36×10^{-5}
Abbreviations: grip, grip strength; SRH, self-rated health. Unmodified P -values are shown for all phenotypes.					

significance for tiredness (Table 2 and Supplementary Table 3) following correction for multiple comparisons. *DRD2* encodes a dopamine receptor and has previously been associated with psychiatric illnesses.⁶³ Alternative splicing of *PRRC2C* has been associated with lung cancer.⁶⁴ Mutations in *ANO10* cause cerebellar ataxias.⁶⁵ *ASXL3* encodes a polycomb protein and mutations in this gene are associated with intellectual disability, feeding problems and distinctive facial features.⁶⁶

In addition, each of these genes was also nominally significant in a GWAS of neuroticism, with *DRD2* being genome-wide significant in both phenotypes.⁴⁹ A comparison with a UK Biobank GWAS of self-rated health²² showed that four of the five genes (*DRD2*, *PRRC2C*, *C3orf84* and *ASXL3*) were significant across phenotypes. Grip strength showed less overlap, with only *C3orf84* being nominally associated with grip strength. Of the five genes examined here, *C3orf84* was associated with each of these four phenotypes. Whereas the genetic correlations between these traits (see below) are likely to encompass multiple genic and non-genic regions, as well as unique points of overlap between pairs of phenotypes, the variants found in the *C3orf84* represent a point of the genome where the genetic architecture of these four traits converges.

Partitioned heritability

From the full baseline model using 52 annotations, only evolutionarily conserved regions were found to be enriched for tiredness (Supplementary Figure 3). This annotation contained only 2.6% of the SNPs from the summary statistics, but they collectively explained 40% of the heritability of tiredness (s.e. = 11%, enrichment metric = 15.34, s.e. = 4.05, $P = 0.0004$). By clustering the histone marks into tissue-specific categories, we found significant enrichment for variants found in the central nervous system (Supplementary Figure 4). This category contained 15% of the SNPs and explained 45% of the heritability (s.e. = 8%, enrichment metric = 3.02, s.e. = 0.54, $P = 0.0002$).

Genetic correlations between tiredness and physical and mental health traits

LD score regression was used to test whether genetic variants associated with health-related traits also contribute towards tiredness in UK Biobank. Table 3 and Figure 3 show these genetic correlations. Positive significant (FDR corrected) genetic correlations were found between tiredness and BMI ($r_g = 0.20$), C-reactive protein ($r_g = 0.17 = 0.02$), HbA1c ($r_g = 0.25$), obesity ($r_g = 0.21$), smoking status ($r_g = 0.20$), triglycerides ($r_g = 0.13$), type 2 diabetes ($r_g = 0.18$), waist-hip ratio ($r_g = 0.28$), attention deficit hyperactivity disorder ($r_g = 0.27$), bipolar disorder ($r_g = 0.14$), major depressive disorder ($r_g = 0.59$), neuroticism ($r_g = 0.62$) and schizophrenia ($r_g = 0.25$). Negative significant (FDR corrected) genetic correlations were found between high-density lipoprotein (HDL) cholesterol ($r_g = -0.11$), forced expiratory volume in 1 s ($r_g = -0.12$), grip strength ($r_g = -0.16$), longevity ($r_g = -0.39$), self-rated health ($r_g = -0.78$) and verbal-numerical reasoning ($r_g = -0.14$). These genetic correlations suggest that there are common genetic associations between tiredness and multiple physical- and mental health-related traits. Supplementary Table 8 shows the genetic correlations between traits associated with the concept of allostatic load (blood pressure, BMI, cholesterol, C-reactive protein, HbA1c, obesity, triglycerides and waist-hip ratio), indicating genetic overlap between these traits.

Polygenic prediction

The full results including all five thresholds can be found in Supplementary Table 4, as well as the number of SNPs included for the five thresholds in each trait. Table 4 shows the results for the polygenic profile scores analyses, using the most predictive

Table 3. Genetic correlations between tiredness documented in the UK Biobank data set and the health-related variables collected from GWAS consortia

Trait category	Traits from GWAS consortia	r_g	s.e.	P
Physical health	Blood pressure: diastolic	0.0332	0.0502	0.5083
	Blood pressure: systolic	-0.0698	0.0478	0.1444
	BMI	0.2024	0.0322	3.18×10^{-10}
	Cholesterol: HDL	-0.1087	0.0373	0.0036
	Cholesterol: LDL	0.0829	0.0413	0.0449
	Coronary artery disease	0.1338	0.067	0.0459
	C-reactive protein	0.0165	0.054	0.0021
	Grip strength ^a	-0.1596	0.0482	0.0009
	HbA1c	0.2536	0.0857	0.0031
	Height	-0.0201	0.0297	0.4980
	Longevity	-0.3943	0.1096	0.0003
	Forced expiratory volume 1s ^a	-0.1181	0.0538	0.0281
	Obesity	0.2063	0.0381	6.31×10^{-8}
	Rheumatoid arthritis	-0.0181	0.0674	0.7885
	Self-rated health ^a	-0.7780	0.0349	7.30×10^{-110}
	Smoking status	0.2009	0.0603	0.0009
	Triglycerides	0.1324	0.0332	6.62×10^{-5}
	Type 2 diabetes	0.1784	0.0689	0.0097
	Waist-hip ratio	0.2834	0.0417	1.09×10^{-11}
	ADHD	0.2694	0.1116	0.0158
Mental health	Alzheimer's disease	0.0762	0.1079	0.4801
	Alzheimer's disease (500 kb)	0.0613	0.0872	0.4816
	Anorexia nervosa	0.0192	0.0492	0.6967
	Autism	0.0129	0.0695	0.8522
	Bipolar disorder	0.1382	0.0605	0.0223
	Childhood cognitive ability	-0.1528	0.0891	0.0864
	Major depressive disorder	0.5902	0.1015	6.03×10^{-9}
	Neuroticism	0.6150	0.038	7.34×10^{-59}
	Schizophrenia	0.2490	0.0386	1.14×10^{-10}
	Verbal-numerical reasoning ^a	-0.1379	0.0596	0.0206

Abbreviations: ADHD, attention deficit hyperactivity disorder; BMI, body mass index; FDR, false discovery rate; GWAS, genome-wide association study; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Statistically significant P -values (after false discovery rate correction; threshold: $P = 0.0281$) are shown in bold. ^aGWAS based on UK Biobank data.

threshold for each trait. Higher polygenic profile scores for 10 physical health traits predicted increased tiredness (significant standardised β 's between 0.008 and 0.026) in UK Biobank: BMI, low-density lipoprotein (LDL) cholesterol, coronary artery disease, C-reactive protein, HbA1c, obesity, smoking status, triglycerides, type 2 diabetes and waist-hip ratio. Higher polygenic profile scores for HDL cholesterol and height predicted lower tiredness (significant standardised β 's between $\beta = -0.016$ and $\beta = -0.008$, respectively).

Of the mental health traits, higher polygenic profile scores for bipolar disorder, neuroticism, major depressive disorder and schizophrenia were associated with increased tiredness (standardised β 's between 0.008 and 0.028). Polygenic profile scores for childhood cognitive ability showed a negative association with tiredness ($\beta = -0.011$).

Sensitivity analysis showed that, when controlling for neuroticism, the associations between tiredness and polygenic profile scores for BMI, obesity, type 2 diabetes, cholesterol (HDL and LDL), C-reactive protein, HbA1c, triglycerides, waist-hip ratio, childhood

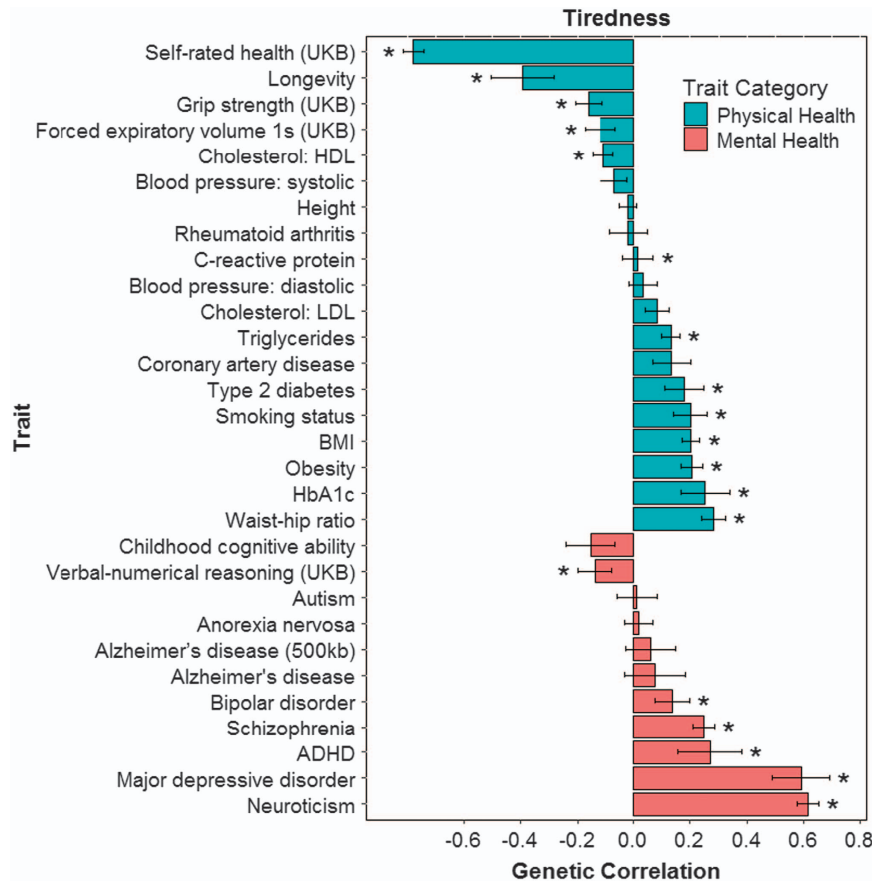


Figure 3. Barplot of genetic correlations (s.e.) calculated using LD regression between tiredness in UK Biobank and mental and physical health measures from GWAS consortia. * $P < 0.0281$. ADHD, attention deficit hyperactivity disorder; BMI, body mass index; GWAS, genome-wide association study; HDL, high-density lipoprotein; LD, linkage disequilibrium; LDL, low-density lipoprotein.

cognitive ability and schizophrenia remained significant (after FDR correction), indicating that these associations are not wholly confounded by scores for neuroticism. Similar analyses controlling for self-rated health indicated that the following associations with tiredness are not wholly confounded by self-rated health: bipolar disorder, neuroticism, major depressive disorder and schizophrenia. Supplementary Table 5 shows the adjusted results and the percentage of attenuation in standardised β 's for the models.

When excluding individuals with a probable diagnosis of major depressive disorder ($N = 7364$) from all individuals with sufficient information about their mental health to make a probable depression diagnosis (full model, $N = 31\,523$), the associations between tiredness and eight polygenic profile scores remained significant (after FDR correction), compared to nine in the full model, the association between type 2 diabetes and tiredness became non-significant after excluding individuals with probable diagnosis of major depressive disorder (Supplementary Table 6). When excluding individuals with a type 2 diabetes diagnosis ($N = 725$), the association between tiredness and the polygenic risk score for diabetes remained significant, indicating that this association is independent of self-reported morbidity for that disorder.

A multivariate regression model including 17 significant polygenic profile scores (BMI, HDL cholesterol, LDL cholesterol, coronary artery disease, C-reactive protein, HbA1c, height, obesity, smoking status, triglycerides, type 2 diabetes, waist-hip ratio, bipolar disorder, childhood cognitive ability, major depressive disorder, neuroticism and schizophrenia) showed that polygenic profile scores for the following traits contributed independently to

the association with tiredness: BMI, HDL cholesterol, triglycerides, waist-hip ratio, childhood cognitive ability, major depressive disorder, neuroticism and schizophrenia. The scores together accounted for 0.25% of the variance in tiredness (Supplementary Table 7).

Age- and sex-stratified analysis

GCTA-GREML analysis was used to test for possible differences in the heritability estimates for tiredness in different age/sex groups. The proportion of variance in tiredness explained by all common genetic variants using GCTA-GREML was 9.4% (s.e. = 1%, $N = 57\,165$) in females and 8.2% (s.e. = 1%, $N = 51\,811$) in males. Figure 4 shows heritability estimates for the three age groups in men and women (40 to < 50, 50 to < 60 years, and 60 to < 70 years). The greatest differences can be seen between males aged 40 and 50 years ($h^2 = 19.8\%$, s.e. = 6%, $N = 10\,798$) and males aged 60–70 years ($h^2 = 3.8\%$, s.e. = 2%, $N = 24\,467$). Genome-wide association analysis indicated no significant sex differences between males and females, but did show some significant age differences in males (Supplementary Figures 5). Genetic correlations between BMI and tiredness were not significantly different for males ($r_g = 0.15$, s.e. = 0.06, 95% confidence interval (CI) = 0.04–0.26, $P = 0.0074$) and females ($r_g = 0.26$, s.e. = 0.05, 95% CI = 0.16–0.36, $P = 4.25 \times 10^{-7}$), as the confidence intervals were overlapping. Also, no significant differences in the genetic correlations were found between waist-hip ratio and tiredness for males ($r_g = 0.30$, s.e. = 0.08, 95% CI = 0.14–0.45, $P = 0.0003$) and females ($r_g = 0.271$, s.e. = 0.06, 95% CI = 0.15–0.40, $P = 2.2 \times 10^{-5}$), with overlapping confidence intervals.

Table 4. Associations between polygenic profile scores of health-related traits created from GWAS consortia summary data, and the UK Biobank tiredness phenotype controlling for age, sex, assessment centre, genotyping batch, and array and 10 principal components for population structure

Trait category	Trait	Threshold	β	P
Physical health	Blood pressure: diastolic	0.1	-0.0028	0.3619
	Blood pressure: systolic	0.1	-0.0025	0.4077
	BMI	1	0.0280	4.90×10^{-20a}
	Cholesterol: HDL	0.5	-0.0163	8.49×10^{-8a}
	Cholesterol: LDL	0.5	0.0081	0.0077^a
	Coronary artery disease	0.5	0.0084	0.0061
	C-reactive protein	1	0.0130	2.10×10^{-5a}
	Forced expiratory volume 1 s	0.01	-0.0059	0.0529
	Longevity	0.05	-0.0067	0.0297
	HbA1c	1	0.0090	0.0033^a
	Height	1	-0.0077	0.0154
	Obesity	1	0.0236	1.20×10^{-14a}
	Rheumatoid arthritis	0.1	-0.0016	0.5926
	Smoking status	0.5	0.0086	0.0071
	Triglycerides	0.5	0.0209	1.06×10^{-11a}
	Type 2 diabetes	1	0.0120	0.0002^{a,b}
	Waist-hip ratio	1	0.0258	7.85×10^{-17a}
Mental health	ADHD	1	0.0042	0.1647
	Alzheimer's disease	0.05	-0.0052	0.0889
	Anorexia nervosa	0.5	0.0048	0.1169
	Autism	1	-0.0018	0.5593
	Bipolar disorder	0.01	0.0081	0.0076^c
	Childhood cognitive ability	0.1	-0.0112	0.0002^a
	Major depressive disorder	1	0.0185	2.25×10^{-9c}
	Neuroticism	0.1	0.0183	2.00×10^{-9c}
	Schizophrenia	1	0.0283	$2.31 \times 10^{-19a,c}$

Abbreviations: ADHD, attention deficit hyperactivity disorder; BMI, body mass index; FDR, false discovery rate; GWAS, genome-wide association study; HDL, high-density lipoprotein; LDL, low-density lipoprotein. FDR-corrected statistically significant values ($P=0.0255$) are shown in bold. The associations between the polygenic profile scores with the largest effect size (threshold) and tiredness are presented. Threshold is the P -value threshold with the largest effect size. ^aResults remain significant after controlling for neuroticism scores. ^bResults remain significant after excluding individuals with type 2 diabetes ($\beta=0.0105$, $P=0.00076$). ^cResults remain significant after controlling for self-rated health.

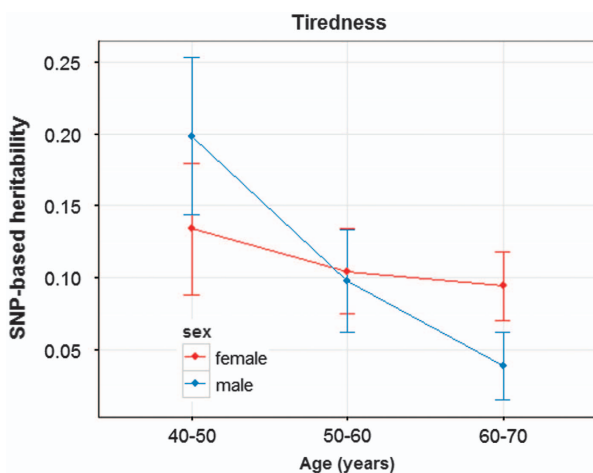


Figure 4. Age- and sex-stratified heritability estimates with s.e.'s for tiredness. SNP, single-nucleotide polymorphism.

DISCUSSION

In the present study, shared genetic aetiology was identified between tiredness and longevity, grip strength, multiple metabolic indicators, smoking status, neuroticism, childhood cognitive ability, depression and schizophrenia. These analyses, combining data from the UK Biobank and many GWAS consortia, provide the first estimate of the overlap in the genetic variants contributing to the heritability of tiredness and these physical and mental health-related traits and disorders. Tiredness demonstrated a significant SNP-based heritability of 8.4%.

In answer to our first research question—is there a direct genetic contribution to self-reported tiredness *per se*?—we found that, whereas there was no large influence on tiredness from common genetic variants, five genes attained genome-wide significance for tiredness: *DRD2*, *PRRC2C*, *ANO10*, *ASXL3* and *C3orf84*. The latter is an uncharacterised protein representing a point of genetic convergence between tiredness, neuroticism, grip strength and self-rated health. *DRD2*, *PRRC2C*, *ANO10* and *ASXL3* have previously been associated with psychiatric illnesses,¹⁸ lung cancer,¹⁹ cerebellar ataxias²⁰ and intellectual disability,²¹ respectively. The three genes within the suggestive peak on chromosome 1 (*CRYZ*, *TYW3* and *SLC44A5*) have previously been associated with insulin resistance, inflammation, risk of type 2 diabetes, metabolism of lipids and lipoproteins, and cardiovascular disease.^{15,16} These genes are consistent with the identification of regions associated with both tiredness and metabolic irregularities, and perhaps more broadly with 'metabolic syndrome' and 'allostatic load'. *PAFAH1B*, within a suggestive peak on chromosome 17 has important roles in brain development.¹⁷ This is consistent with the identification of regions associated with both tiredness and cognitive traits, and the finding of significant enrichment for variants found in the central nervous system.

Evolutionarily conserved regions were found to be enriched for association with tiredness, consistent with findings for other quantitative traits including disease status,⁵³ suggesting that these are important loci where common additive SNPs cluster to produce phenotypic variation in many traits, as explored in more detail in the paper by Hill *et al.*⁶⁷ The range of factors— affective, cognitive, behavioural and physical—that are genetically associated with tiredness is in itself remarkable, and confirms the observation of Landmark-Høyvik *et al.*,³⁴ quoted in the introduction, that the related construct of fatigue is aetiologically

heterogeneous and multifactorial. No overlap has been found with genes (*GRIK2*, *NPAS2*) identified in previous GWAS of fatigue;^{39,40} however, the sample size of these studies was too small to have enough power to detect statistically significant differences. The present study did not show significant associations for candidate genes previously identified.³⁴

The results of the present study add to the body of evidence that tiredness has a genetic underpinning.^{35,36,38} This study estimated the SNP-based heritability of self-reported tiredness at 8.4%, and also examined age- and sex-specific heritability. No differences were found between males and females, but the results suggested a higher heritability in males aged between 40 and 50 years, compared to males between 60 and 70 years. Previous twin studies have shown inconsistent results regarding the sex-specific heritability. One study reported a higher heritability for prolonged fatigue (fatigue for more than one month) in males,³⁶ whereas another reported a higher heritability for 'interfering' fatigue (fatigue for >5 days) in females.³⁵ One study reported no sex differences in the heritability of chronic fatigue.³⁶ In summary, the answer to our first question is that, whereas tiredness is, as expected, largely causally heterogeneous, there may be a small but significant, direct genetic contribution to tiredness proneness.

In answer to question two—is tiredness genetically linked to proneness to health-related traits?—we can answer in the affirmative. The range of factors—ffective, cognitive, behavioural and physical—that are genetically associated with tiredness is in itself remarkable, and confirms the observation of Landmark-Høyvik *et al*,³⁴ quoted in the introduction, that the related construct of fatigue is aetiologically heterogeneous and multifactorial. This may seem a relatively trivial finding whether we assume that it simply reflects the sum of genetic factors that are primarily associated with other more specific phenotypes, which cause tiredness in one way or another. However, it is important to recall that the biobank data capture illness propensity rather than actual morbidity. In our sensitivity analysis, we controlled for the presence of type 2 diabetes and found that the genetic link between type 2 diabetes and tiredness remained significant. This would indicate that, for this health marker at least, tiredness and illness proneness are genetically related irrespective of the presence of morbidity. Similarly, the genetic association between tiredness and longevity would argue for a non-trivial link between self-reported tiredness and a more general tendency to poor health.

This takes us into the territory of question three—is tiredness genetically linked to a systemic proneness to poor health? To begin to answer this, we examined the genetic associations between tiredness and putative markers of allostatic load. Tiredness showed significant shared heritability with a range of factors associated with the metabolic syndrome⁶⁸ including cholesterol, triglycerides, HbA1c, waist-hip ratio, BMI, obesity and type 2 diabetes. Several of these factors are biomarkers of allostatic load.^{61,62} The concept of allostatic load has been used in the context of both physical and mental ill health, including the symptom of fatigue. Conceptually, allostatic load represents the cumulative, physiological 'wear and tear' of a prolonged response to a stressor. Allostatic load has been shown to be a reliably-measurable multi-variate construct,^{69,70} with first-order factors comprising cardiovascular, immune, metabolic, anthropometric and neuroendocrine markers.²⁹ It is hypothesised that, in response to threats to homeostasis, the body's self-regulatory mechanisms, such as the sympathetic-adrenal medullary axis and the hypothalamic pituitary adrenal axis, have the potential to 'over-compensate and eventually collapse upon themselves',²⁹ with consequences for morbidity and mortality.

In our current analysis, we included metabolic (cholesterol, HbA1c and triglycerides), anthropometric (waist-hip ratio, BMI and obesity) and cardiovascular/respiratory (diastolic and systolic

blood pressure, and forced expiratory volume) markers of allostatic load. The results showed significant shared genetic aetiology, as measured by both LD score regression and polygenic profile score analysis, between tiredness and most of the metabolic and anthropometric markers, though not the cardiovascular/respiratory markers. This raises the possibility that the genetic overlap between tiredness and these physiological factors may be due to a biological propensity to an over-compensatory physiological stress response. This suggestion will require further investigation, because a more parsimonious explanation of these links would be that there is a genetic link between tiredness and multiple, separate genetic determinants of poor physical health. However, the substantial genetic correlations between these traits, and between these traits and tiredness provide some evidence that the allostatic load concept does have coherence at the genetic level.

Fourth, to answer the question on the genetic associations between tiredness and the personality trait of neuroticism, which is the tendency to experience negative affective states, these were indeed strongly correlated, both phenotypically and genetically. This may represent a separate route to fatigue, a predominately affective one, and/or it may overlap with the physiological factors described above. A recent paper by Gale *et al*,⁴⁹ also using this UK Biobank sample, supports that the physiological and affective dimensions of poor health overlap in neuroticism. That paper showed that polygenic profile scores for several physical and mental health traits—BMI, coronary artery disease, smoking status, bipolar disorder, borderline personality, major depressive disorder, negative affect and schizophrenia—significantly predicted neuroticism. In the present study, when tiredness polygenic profile score analyses were adjusted for neuroticism, the associations between tiredness and mental health disorders (bar schizophrenia) were largely attenuated, whereas most of the metabolic and anthropometric associations remained significant. This suggests that it is the propensity to neuroticism, rather than the specific propensity to these disorders, that accounts or mediates the tiredness associated with mood disorders. Watson and Pennebaker,⁷¹ discussing competing models of how negative affectivity is related to self-reported physical and emotional well-being, found that it is associated as much with the former as with the latter, and that negative affectivity might better be conceptualised as a general tendency to experience both somatic and emotional distress. This concept of a general tendency to what they termed somatopsychic distress could explain the pleiotropy observed in the present study between neuroticism and tiredness.

That neuroticism may also be a distinct route to fatigue is supported by the fact that when the polygenic profile score analysis is adjusted for self-rated health, all associations between polygenic profile scores for physical health and tiredness are attenuated to the point of non-significance, whereas the relationship between tiredness, and polygenic profiles for neuroticism, major depressive disorder and bipolar disorder remain significant. This is consistent with the study of Gale *et al*,⁴⁹ investigating shared genetic aetiology between neuroticism and physical and mental health, where there were more and stronger genetic associations between neuroticism and mental health than between neuroticism and physical health. If we take self-rated health to be a marker, to some extent, of actual physical health (and the study by Harris *et al*.⁴⁸ would indicate that it is), then this would suggest that when physical health is adjusted for, polygenic profile scores for neuroticism and its associated negative affective states, continue to make a unique contribution to tiredness.

These proposed affective and physiological routes to fatigue may not be mutually exclusive. The allostatic load model, and the multifactorial models of fatigue described in the introduction, postulate that individual differences in personality, cognition and behavioural responses to stress, and socio-cultural factors, affect the physiological stress response. An increased propensity to

experience distress, as captured in the concept of neuroticism, would imply that there is increasing propensity to over-respond to stressors and thus to physiological dysregulation. In the study by Gale *et al.*,⁴⁹ the only significant result between neuroticism and physical disease state was a significant association with the polygenic risk score for coronary artery disease, which is suggestive of an overlap of affective and cardiovascular stress responses. This multifactorial understanding of fatigue would also allow us to incorporate childhood cognitive ability (reduced ability to problem solve), smoking status (at least one study has found smoking and allostatic load interaction effects²⁹) and grip strength (reduced overall system integrity/vigour) into a more general model that is suggestive of shared genetic variance between stress proneness (neuroticism, reduced cognitive ability and reduced vigour), the physiological response to stress (biomarkers), behavioural responses (smoking), self-reported tiredness, disease and mortality.⁷² However, as with our discussion of allostatic load, these links are suggestive not conclusive, and will require further empirical and theoretical investigation.

The large sample size of the present study is a strength of this study, providing powerful and robust tests of shared genetic aetiology between tiredness, and physical and mental health. A second strength is that all genetic samples were processed on the same platform at the same location. The use of summary data from many international GWAS consortia provided foundations for a comprehensive examination of shared genetic aetiology between tiredness and a wide range of health-related phenotypes.

The study has some limitations. The amount of variance explained by the polygenic profile score analysis was small, which would be expected as not all SNPs are genotyped. The SNPs that were genotyped do not necessarily accurately tag the causal genetic variants. All analyses were restricted to individuals of white British ancestry, because the sample does not have enough power to generalise results for individuals with different backgrounds. Also, the sample consisted of middle- and older-aged adults, thus limiting its generalisability to the adult population as a whole. However, as mentioned in the introduction, there are no clear age-related differences in levels of self-reported fatigue. This could be taken as an indication that the phenomenon is fairly stable across the adult life course, at least at the level of phenotype. Whether the genetic determinants are different in younger adults is a topic for future research.

A further limitation of the present study is the fact that tiredness was measured by self-report; that is, that we were looking for objective correlates of a subjective construct. However, as Wessely⁷³ observed, an objective measure of fatigue is 'an unattainable holy grail'. Almost all the studies cited in the introduction have used subjective self-reports. The self-report measures used vary widely, with there being several validated fatigue measures, and many of the reported studies use either double- or single-item questionnaires and/or single item visual analogue scales. This in itself may account for some of the inconsistency in fatigue research, though the demographic studies cited at the beginning of this article, using a wide variety of measures from single questions⁷ to a well-validated fatigue questionnaire,² produced similar findings. However, our findings of genetic associations of fatigue will need replication with better validated multi-item measures.

Perhaps a more serious concern is the one signalled in the introduction: that fatigue is too causally heterogeneous a trait to meaningfully study at the genetic level. To address this, it is worth situating this research in the context of other recent and ongoing fatigue research, such as the recently announced National Institute of Health Mechanisms of Fatigue programme. The latter, while acknowledging that fatigue 'is a common co-morbid condition in a multitude of disease conditions', is attempting to define whether 'molecular, cellular or imaging signatures of fatigue can be defined'.⁴² Like the psychosocial and biological fatigue research

cited in our introduction, this work is predicated on the notion that, whereas fatigue shows up as a response to many physical and psychosocial stressors, its determinants may be shared across conditions. As such, we should distinguish between the effective cause of fatigue (the illness/stressors that set it going), and the material and formal causes (the bodily and psychosocial processes that produce and maintain the phenomenon).⁷⁴ Whereas the effective causes might be various, the material and formal causes are likely to be more limited and shared across individuals and precipitating conditions. Even if this is not the case, we judge that the present study has gone some way to specifying the nature of the heterogeneity of tiredness at the genetic level, and that there are several non-trivial insights that will require further investigation, specifically: the links between tiredness and illness proneness as distinct from actual morbidity; the genetic coherence of the allostatic load concept and its contribution to tiredness; and the nature of the shared genetic and phenotypic links between tiredness and the personality trait of neuroticism. In terms of the genetic contributions to this complex phenomenon, the current study is probably best seen as the first attempt to use a large and relatively well-powered GWAS to identify these areas for future research.

Summary

Being genetically predisposed to a range of mental and physical health complaints also predisposes individuals to report that they are more tired or lacking in energy. This study confirms that self-reported tiredness is a partly heritable, heterogeneous and complex phenomenon that is phenotypically and genetically associated with affective, cognitive, personality, health and physiological processes. This study also served as a first step in testing some genetic hypotheses from the allostatic load model, finding suggestive links between tiredness and three genes on chromosome one associated with allostatic processes and considerable genetic overlap between tiredness and allostatic markers. We can foresee more tests of these links as more genome-wide genotyping data become available.

CONFLICT OF INTEREST

IJD is a participant in UK Biobank. The remaining authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (<http://www.nature.com/mp>)

7.3. Conclusion

The study in Section 7.2 by V. Deary et al. (2017) showed genetic contributions to self-reported tiredness/low energy, a measure related to negative emotions, as well as extensive shared genetic aetiology between self-reported tiredness and the physical and mental health variables studied here. The genetic overlap was particularly strong with neuroticism, major depressive disorder, and self-rated health. Taken together with the work presented in Chapter 6, these results support the idea that self-reported variables related to negative emotions, such as neuroticism and tiredness, capture the concept of general somato-psychic distress (Watson & Pennebaker, 1989), and that this is linked to poorer general health. The next Chapter will provide a general discussion of the work presented in this thesis.

Following online publication of this paper, the authors noticed a mistake in Table 3 and Figure 3, and in Table 4. The genetic correlation between tiredness and C-reactive protein was displayed as 0.0165, but the correct genetic correlation is 0.1650. The thresholds for major depressive disorder and neuroticism are incorrect in Table 4. The threshold for major depressive disorder is 0.1, and for neuroticism the threshold is 1, as displayed in the corrected Table 4. A corrigendum is in press at the time of writing.

8. Discussion

8.1. General findings

The present Thesis examined the extent to which the phenotypic associations between cognitive ability and health, and between negative emotions and health are due to shared genetic influences. This was assessed in the large UK Biobank cohort using linkage disequilibrium score regression (LDSR) and polygenic risk analysis (PRS) analysis, and other molecular genetic techniques. This final Chapter discusses the findings in this thesis in light of the two main objectives, considers both methodological and sample limitations, and will finish by discussing implications for future research.

8.1.1. Cognitive ability

The first objective of this thesis was to examine the shared genetic aetiology between cognitive ability and mental and physical health. The results in Chapter 4 provide evidence for genetic overlap between different measures of cognitive ability and a range of health outcomes. Using LDSR and PRS analysis, both verbal-numerical reasoning and college degree attainment were positively associated with autism, intracranial volume, childhood cognitive ability, and educational attainment, and negatively with ischaemic stroke, Alzheimer's disease and body mass index (BMI). A negative association was found between schizophrenia and all cognitive phenotypes, except college degree attainment, which showed a positive association. College degree attainment was positively associated with bipolar disorder, infant head circumference, and height. A negative association was reported between college degree attainment and coronary artery disease.

One of the previously described underlying mechanisms for the association between cognitive ability and health was the theory of bodily system integrity (Section 1.2.4). This theory

proposes that better cognitive ability could be a marker for a latent trait of a well-functioning body. Both biological and mediated pleiotropy provide support for this theory. The association between cognitive ability and health could be caused by genetic variants that have an effect on both cognitive ability and health outcomes, i.e. biological pleiotropy. In the case of mediated pleiotropy, it is possible that genetic variants associated with better cognitive ability causes better lifestyle, higher education, and better socio-economic status, which are all associated with better health outcomes. This would be a more sensible idea when taking into account the association between educational attainment and health, as one would never expect to find genes directly related to educational attainment as this is not a biological trait.

These associations were all in the expected direction, with poor health being associated with lower cognitive ability, except the association between college degree attainment and schizophrenia and autism, which indicated that higher genetic risk for schizophrenia and autism is associated with higher chance of college degree attainment. The association between educational attainment and schizophrenia is supported by a study that showed a small positive genetic correlation between the two (Okbay et al., 2016b). The study by Okbay et al. (2016b) used the same GWAS summary data for schizophrenia, based on the Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014), but educational attainment was based on years of education and measured in an independent sample. Further evidence supporting the positive genetic association of educational attainment with schizophrenia, as well as with autism, has been reported by Warrier, Bethlehem, Geschwind, and Baron-Cohen (2016). They reported significant enrichment of educational attainment genes in both schizophrenia and autism co-expression modules. The authors suggest that genes for educational attainment possibly interact with schizophrenia and autism genes in different ways, for example at transcriptome level, and the interactions could potentially lead to both cognitive deficits and cognitive talents in schizophrenia and autism. However, conclusions about directions of effect cannot be made from these findings.

Bansal et al. (2017) showed the clinical diagnosis of schizophrenia likely consist of two disease subtypes with different genetic aetiologies, one more similar to bipolar disorder and high cognitive ability, and the other resembling a cognitive disorder. These results support the positive genetic association between educational attainment and both schizophrenia and autism, as reported in Section 4.2. Positive selection of autism risk alleles has been reported by Polimanti and Gelernter (2017), and these alleles were enriched for biological processes related to neural development. Based on these findings the authors suggest that autism risk alleles could positively affect behavioural traits related to brain development, which could lead to better cognitive ability in carriers of the autism risk alleles.

Limited evidence was found for shared genetic aetiology between reaction time, memory and health outcomes. Reaction time was negatively associated with major depressive disorder (MDD), while memory showed a negative association with bipolar disorder and a positive association with BMI. The SNP-based heritability estimates for both reaction time and memory in UK Biobank are 11% and 5%, respectively (G. Davies et al., 2016b), indicating that only a small proportion of the variance in test scores can be explained by genetic influences. It is therefore unsurprising to find limited evidence for a shared genetic aetiology of these two phenotypes and health outcomes, due to both tests being very short and the memory test having a poor reliability, which will be discussed in more detail in Section 8.2.2.

Using a bidirectional Mendelian randomization approach, we next examined potential causal association between cognitive ability and health. Specifically, we examined if educational attainment, a proxy phenotype for cognitive ability, causally influences physical health, or if physical health outcomes causally influence cognitive ability (Section 4.3). No evidence for a causal association in either direction was found.

Two recent studies tested for causal effects of educational attainment on health outcomes (N. M. Davies, Dickson, Davey Smith, van den Berg, & Windmeijer, 2016; Tillmann et al., 2017). N. M. Davies et al. (2016) used the raising of the school leaving age from 15 to 16 years in September 1972 as a natural experiment to test for causal effects of staying in school in UK Biobank. A genome-wide genetic risk score for educational attainment was created to estimate the effects of attending school on health outcomes. The results showed that remaining in school past the age of 15 years is associated with reduced risk of diabetes, stroke, heart attack, and mortality, lower BMI and systolic blood pressure, and increased grip strength and income. No sensitivity analyses, such as Mendelian randomization Egger regression, have been performed on these results; it is therefore possible that these results are biased by pleiotropic effects of the genetic variants. Tillmann et al. (2017) used a two-sample MR analysis to assess the causal effects of educational attainment on coronary artery disease and cardiovascular risk factors. A two-sample MR analysis uses GWAS summary results from two independent consortia and thereby increases statistical power. The results reported by Tillmann et al. (2017) showed that a 1 SD increase in educational attainment (3.6 years) was associated with a 33% decrease in risk for coronary artery disease, as well as decreased risk for cardiovascular risk factors such as smoking, BMI, and blood lipids. Sensitivity analyses indicated that the results were not biased by pleiotropic effects. While our study did not indicate causal associations between cognitive ability, or educational attainment, and health, two more recent studies did show a causal relationship, where more time spent in school decreases risk for disease.

The introduction of the Trail making test (TMT) during the web-based assessment in UK Biobank provided the opportunity to compare the genetic architecture of the TMT measure with the genetic architecture of other cognitive measures. TMT is an important neuropsychological test for executive functioning and it is widely used in clinical settings to test for performance deficits in for example mental health disorders. Multivariate behavioural genetic studies have shown that a common genetic factor underlies the correlational structure

between cognitive measures (T. Lee et al., 2012; Vasilopoulos et al., 2012). T. Lee et al. (2012) also identified a genetic correlation between TMT and general cognitive ability of 0.48 in a behavioural genetics study of 472 twins. These previous findings support the molecular genetic findings as discussed in Chapter 5, showing substantial genetic overlap between TMT and general cognitive ability and processing speed. In Chapter 4, we identified shared genetic aetiology between measures of cognitive ability in UK Biobank and health outcomes. While all three cognitive measures, verbal-numerical reasoning, reaction time, and memory, were bespoke non-standardized test, the reaction time and memory test had particularly problematic psychometric properties (Lyll et al., 2016). While the study in Chapter 5 did not directly test for a genetic association between TMT and health, the genetic overlap between the standardized TMT measure and verbal-numerical reasoning in UK Biobank, as well as the overlap with general cognitive ability and processing speed, might aid in the understanding of the complex relations between cognitive ability and health outcomes.

To answer the first key question of this thesis, using different molecular genetic techniques, shared genetic aetiology was identified between cognitive ability and mental and physical health. Mendelian randomization analyses did not identify causal associations between cognitive ability and physical health. The next Section of this Discussion will summarize the findings of Chapter 6 and 7.

8.1.2. Negative emotions

The second objective of this thesis was to examine the shared genetic aetiology between negative emotions and physical and mental health. For this thesis, both the personality trait of neuroticism and fatigue (assessed using a question about tiredness and low energy) were used as measures of negative emotions. As reported in Chapter 6, both LDSR and PRS analysis showed positive genetic associations between neuroticism and anorexia nervosa, MDD, and

schizophrenia. PRS analysis alone identified that higher PRS for bipolar disorder, borderline personality disorder, anxiety, coronary artery disease, and smoking were associated with higher neuroticism scores. Higher PRS for BMI was associated with lower neuroticism scores, while based on the phenotypic association one would expect a higher PRS for BMI to predict lower neuroticism scores. Krapohl et al. (2016) did not find a significant association between polygenic risk for BMI and neuroticism, in a sample of 3152 individuals, but the direction of effect was negative, similar to the study in Chapter 4. No significant genetic correlation was found using LDSR in either UK Biobank or the Genetic of Personality Consortium in the current study. Okbay et al. (2016a) also did not identify a significant genetic correlation between neuroticism and BMI. This could indicate that the negative association between BMI polygenic risk and neuroticism is a false positive. Overall, the genetic associations between neuroticism and mental health traits provide further evidence for the idea that personality and mental health are related to each other.

When examining fatigue, using self-reported tiredness/low energy, the previously identified positive genetic association between neuroticism and MDD and schizophrenia were also identified between tiredness and MDD and schizophrenia, as shown in Chapter 7. Using LDSR and PRS analysis, further positive genetic associations were found between tiredness and BMI, C-reactive protein, HbA1C, obesity, smoking, triglycerides, type 2 diabetes, waist-hip ratio, bipolar disorder, and neuroticism. A negative association was found between tiredness and HDL cholesterol. LDSR alone identified negative genetic correlations between tiredness and longevity, grip strength, self-rated health, forced expiratory volume in 1, and verbal-numerical reasoning. The correlation with the last four phenotypes could not be analysed using PRS analyses, as these traits originated from UK Biobank, and PRS analysis requires independent samples.

One of the theories to explain the associations between negative emotions and health, suggests that negative emotions correlate with subjective health complaints, rather than actual physical health disorders. This is often referred to as ‘the symptom perception’ hypothesis (Costa & McCrae, 1987; Watson & Pennebaker, 1989). The phenotypic associations between negative emotions and self-rated health, as reported in the current thesis and by Harris et al. (2016a) showed that a higher level of negative emotions was correlated with lower self-rated health, which would support the symptoms perception hypothesis, as self-rated health is a subjective measure of one’s health. Self-rated health, however, does actually capture genetic contributions to mental and physical health disorders (Harris et al., 2016a). Combined with the results reported in this thesis—i.e., a shared genetic aetiology between negative emotions and health—these findings support an association between negative emotions and physical health disorders, instead of only subjective health complaints. This suggest that the symptom perception hypothesis does not fully explain the association between neuroticism and health.

As previously discussed in the discussion of Chapter 7, neuroticism and tiredness showed a phenotypic correlation of 0.39 and a genetic correlation of 0.62. Both showed a shared genetic aetiology with mental health disorders such as major depressive disorder and schizophrenia. This suggests that the genetic influences on both neuroticism and tiredness are due in part to common processes. These findings, therefore, provide support for the idea that negative emotions are a measure of somatopsychic distress, as suggested by Watson and Pennebaker (1989).

To answer the second key question of this thesis, using different molecular genetic techniques, some shared genetic aetiology was identified between negative emotions and mental and physical health. The two measures of negative emotions, the personality trait of neuroticism and self-reported tiredness, were strongly associated on both a phenotypic and genetic level. The next Section of this Chapter will discuss the potential limitations of findings in this Thesis.

8.2. Limitations

Study specific limitations have been discussed in each of the corresponding Chapters, this Section will therefore focus on general methodological and sample limitations of the current Thesis.

8.2.1. Methodology

Several methodological limitations should be considered in this Thesis. Firstly, as briefly discussed in Section 5.2.4, heritability estimates based on genotype data are generally lower than heritability estimates based on twin and family studies. SNP based heritability estimates are based on LD between genotyped variants and low LD between genotyped and causal variants might lead to lower heritability estimates. Heritability estimates based on twin and family studies are based on identity-by-descent (IBD), which refers to alleles that have been inherited from a common ancestor. Regions of IBD between pairs of individuals will share all genetic variants except *de novo* mutations (Powell, Visscher, & Goddard, 2010). Twin and family studies are therefore likely to capture more of the genetic contributions to a trait. Hill et al. (2017) have shown that the difference in heritability estimates for general cognitive ability between the two methods is due causal variants being in low LD with genotyped SNPs, by using a family design. For neuroticism, the authors did not identify the cause of the differences between the twin and SNP-based heritability estimates, which supports the idea that non-additive genetic components play a major role in the aetiology of neuroticism.

Secondly, PRS are limited by the strength of the association in the original GWAS. Several of PRS used in this Thesis (brain phenotypes, stroke) are based on relatively small samples and are therefore potentially limited in statistical power to accurately predict the outcome (Dudbridge, 2013). It is also important to note that sample overlap between UK Biobank and

some of the GWAS consortia might have led to an overestimation of the associations. Where possible, we have excluded overlapping participants, for example 174 individuals from GS:SFHS are also part of UK Biobank; these individuals were excluded from GS:SFHS prior to any analysis that involved PRS based on UK Biobank data. For most of the data used for PRS, it was impossible to quantify the exact overlap, but we expect this to be minimal.

Finally, all studies in this Thesis were based on individuals of White British ancestry, and the results are therefore not generalizable to other populations. The majority of GWAS have been performed in European populations due to the wide availability of reference panels based on European ancestry, such as the 1000 Genomes Project (The 1000 Genomes Project Consortium, 2010) and the International HapMap Project (The International HapMap 3 Consortium, 2010; The International HapMap Consortium, 2007), and the availability of large European ancestry cohorts. As mentioned in Section 1.3.2.4, the LD structure differs between ethnic populations, the efficiency of reference panels based on European ancestry is therefore less efficient in other populations. While there are imputation reference panels available for other populations, for example from the International HapMap Project, the number of cohorts with non-European ancestry is limited. The full UK Biobank sample consists of 94% of individuals with a White background (UK Biobank, 2015b), the other populations consisted of relatively small subgroups, it was therefore not possible to have performed GWAS on other populations in order to replicate our findings in different populations, due to a lack of power. A recent study showed that PRS based on a GWAS of European ancestry individuals did not perform well in individuals of African ancestry (Ware et al., 2017); in individuals of European ancestry PRS were associated with the trait of interest in 80% of the cases, while in individuals of African ancestry these PRS were only associated with the trait of interest in 5% of the cases, based on an α of 0.001.

8.2.2. UK Biobank

One of the main limitations of UK Biobank is the use of bespoke cognitive tests. As previously shown by Lyall et al. (2016), the measures of reaction time and memory have particularly poor psychometric qualities. The measure of reaction time in UK Biobank consisted of four trials, whereas measures of reaction time generally include at least 20 to 40 trials (I. J. Deary et al., 2001; Der & Deary, 2006). The memory tested consisted of two versions, one using a 2x3 grid and one using a 3x4 grid. As shown in Figure 3-8, the 2x3 grid displays a ceiling effect, with nearly three quarters of the sample making no errors in identifying the three matching pairs. The 3x4 grid does not show such a clear ceiling effect but has a very poor test retest reliability of 0.15 over a period of two to seven years. These psychometric limitations potentially explain the lack of results for these measures. When comparing the measures in UK Biobank with standardized well validated cognitive measures in the LBC1936, educational attainment PRS explain 3% of the variance in general cognitive ability in LBC1936, while educational attainment PRS in UK Biobank only explain 1% of the variance in the test most similar to general cognitive ability, verbal-numerical reasoning (G. Davies et al., 2016b).

Secondly, the UK Biobank sample is oversampled for older individuals with higher educational attainment and a better socio-economic status, compared to the general population in the United Kingdom. UK Biobank has a lower proportion of individuals aged 40 to 55 years, and a higher proportion of individuals aged 55 years and older compared to the 2011 Census data, as shown in Figure 3-2. When comparing the Townsend deprivation index, there were fewer individuals from the very deprived areas and more from the very high SES areas. It is important to note that the Townsend deprivation index was based on the 2001 Census data, as the Townsend deprivation index is not yet available for the 2011 Census. Individuals in UK Biobank are 1.6 times more likely to have a degree compared to the 2011 Census data. Generally, population, family, or twin studies include individuals with higher average

cognitive abilities than the general population. This could potentially lead to inflated heritability estimates (Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003), because these cohorts do not sample the whole distribution of cognitive ability. It also means that the results reported in this Thesis are not fully generalizable to the general population.

Disease status was ascertained during the touchscreen questionnaire based on self-report; all participants were asked if a doctor ever told them they had a certain diagnosis. If the participant answered affirmative or that they did not know, a trained nurse followed up during a verbal interview to confirm possible diagnoses. This could be problematic, particularly in the case of diabetes mellitus. The touchscreen questionnaire only asked if participants were diagnosed with diabetes in general; during the verbal interview participants could be specific about the type of diabetes they were diagnosed with (for example, type 1, type 2, gestational, or diabetes insipidus). Participants were also asked when they were diagnosed with diabetes, and when they started insulin treatment. In practice, this means that there are different ways to compute diabetes case control status. The sensitivity analysis in Chapter 7 used a conservative approach and only included individuals who answered that they were diagnosed with diabetes in the touchscreen interview and confirmed that it was type 2 diabetes in the verbal interview ($n = 725$). For the analysis in Section 4.3, we adopted a less conservative approach, as described in Section 4.3.2.2, based on Yaghootkar et al. (2016), which lead to 3764 cases of type 2 diabetes. It is therefore possible that we underestimated the number of cases and the effect of type 2 diabetes on our results in Chapter 7. UK Biobank have recently updated their data showcase and included algorithmically defined cases of myocardial infarction and stroke, based on a combination of self-report data and hospital records. It would be useful to have similar case-control ascertainment for other diseases, such as type 2 diabetes.

While UK Biobank certainly has several important limitations, one should not forget the strengths of this sample. It is currently the largest single sample population study including

over 500,000 individuals, with an interim release of genetic data for 150,000 individuals. All individuals in UK Biobank have been tested using the same measures and heterogeneity in sample composition, cognitive measurement and genetic testing, as can be found in large consortia cohorts will be therefore be minimal.

8.3. Future research

Future studies should focus on replicating the results reported in this Thesis, in particular between negative emotions and health, as many of these associations have not been reported previously. In order to better understand the underlying mechanisms of these associations, it is important to untangle causal phenotypic pathways and identify biological pathways.

The availability of the full release of UK Biobank genetic data, in the second quarter of 2017, will provide an opportunity to further identify causal pathways between cognitive ability, negative emotions and health. This release will also improve the predictive value of PRS; the large sample of 500,000 individuals could be split in to two, where one part could be used for GWAS of a trait of interest, and the other part could be used as the prediction sample. This would be particularly useful for traits that do not have publicly available GWAS summary statistics. The verbal-numerical reasoning test and the trail making test, are at the moment likely the most well validated cognitive measures in UK Biobank. Because both have been added at a later stage during assessment, only a subset of the whole sample completed these tests. The release of the full data will increase the sample size for these tests from ~36,000 to ~185,000 individuals for verbal-numerical reasoning and from ~23,000 to ~ 120,000 for the Trail making test. The findings reported in Chapter 4 and Chapter 5 could be used to address the overlap between executive function and health outcomes using this larger sample, to further disentangle the complex web of associations between cognitive ability and health. This

full release will also provide the opportunity to use longitudinal data to better examine the causal associations between cognitive ability, negative emotions and health.

Based on the limitations discussed in the previous section, improvement of the cognitive measures in UK Biobank would be of great value. Dementia's Platform UK is currently working on a new set of enhanced cognitive measures, which will be added to UK Biobank in due course and will include measures of verbal declarative memory, subjective memory, executive function, vocabulary, and non-verbal reasoning (Fawns-Ritchie, 2016). While it would be preferred to have extensive cognitive testing such as in LBC1936, this would not be feasible for a large cohort as UK Biobank, due to the associated costs and time it would take to test all participants.

The availability of molecular genetic methods has changed rapidly in the past three years and has not stopped changing. This means that newer and better techniques can be used on the same data, for example to examine causal pathways, which will improve power to detect associations. Whereas the current Thesis has focussed on the release of genetic data in UK Biobank, imaging data has also been released. UK Biobank is planning to release imaging data for 100,000 individuals in the future, currently data for about 11,000 individuals is available. This provides the exciting opportunity to link brain imaging with genetics data, which will be especially useful in the case of cognitive ability, a trait highly linked to brain function.

As indicated by the results in this Thesis, genetic variants explain part of the association between cognitive ability and health, and between negative emotions and health. To improve the predictive value of these associations, future studies could combine genetic information with biomarkers, environmental risk factors, and brain imaging data. This could move the field towards precision medicine and will help develop new diagnostics and therapeutics, especially in the case of mental health traits.

The studies in this Thesis made use of a wide range of PRS. In future research, PRS could be used to identify individuals at high risk for disease in both clinical trials and prevention studies. Increasing the accuracy of identifying high risk individuals in clinical trials using PRS will likely lead to a better chance of success. On the other hand, PRS can be used to identify individuals at the other end of the PRS distribution, to identify controls at very low risk of disease. In the case of prevention studies, identifying individuals at different risk levels for disease could be used to tailor interventions according to risk, especially when combining genetic risk with environmental risk factors.

The findings presented in this Thesis could provide a first step in further disentangling biological causal pathways between cognitive ability, negative emotions, and health. A better understanding of the shared genetic aetiology between these traits could help policymakers to link changes in cognitive ability or negative emotions to harmful biological changes in the body, which in future will aid to better understand and address health inequalities. On the other hand, better understanding of causal pathways between cognitive ability, negative emotions, and health could potentially provide new drug targets or inform on new purposes for known drug targets.

8.4. Final summary

The main focus of this thesis was to investigate the potential shared genetic aetiology between cognitive ability and health, and between the tendency to experience negative emotions and health. Additionally, we tested how the important neuropsychological Trail making test was associated with other measures of cognitive ability. We identified extensive genetic overlap between verbal-numerical reasoning, educational attainment and mental and physical health traits, and made a start to untangle to causal pathways between cognitive ability and health.

The trail making test showed strong genetic overlap with measures of general cognitive ability and processing speed. Negative emotions, measured by neuroticism and self-reported tiredness/low energy, also showed genetic overlap with health outcomes. Neuroticism was mainly associated with mental health, while self-reported tiredness showed genetic overlap with both mental and physical health. Taken together, the results in the present Thesis provides further evidence for, and better understanding of, associations between cognitive ability and health, and between negative emotions and health. Progress in these research areas will help us better understand the causes of disease, but will also potentially help preventing disease in the population in the long term.

9. References

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Appendices

Appendix 1. Supplementary material to Section 4.2

Supplementary Materials for:

Hagenaars et al. Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N = 112 151) and 24 GWAS consortia

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Supplementary Table 1

For each health-related phenotype for which we use genome-wide association study summary data, here are some key example references showing its relation to prior cognitive function (left-hand column) and its possible effects on later cognitive function (right-hand column). (-) indicates a negative association with cognitive function, while (+) indicates a positive association with cognitive function.

Link to prior cognitive function	Phenotype	Effect on cognitive function
Vascular-metabolic diseases		
Lawlor et al. (2008). (-)	Coronary Artery Disease	Kovacic et al. (2012) (-) Eggermont et al (2012) (-)
Lawlor et al. (2008) (-) Rajan et al. (2014) (-)	Stroke: Ischaemic	Brainin et al. (2015) (-)
Lawlor et al. (2008) (-) Rajan et al. (2014) (-)	Stroke: Cardioembolic	Brainin et al. (2015) (-)
Lawlor et al. (2008) (-) Rajan et al. (2014) (-)	Stroke: Large Vessel Disease	Brainin et al. (2015) (-)
Lawlor et al. (2008) (-) Rajan et al. (2014) (-)	Stroke: Small Vessel Disease	Brainin et al. (2015) (-)
Möttus et al. (2013) (-)	Type 2 Diabetes	Rawlings et al. (2014) (-)
Neuropsychiatric disorders		
N/A	ADHD	Frazier et al. (2004) (-)
Whalley et al. (2000) (-)	Alzheimer's Disease	N/A
N/A	Autism	Fombonne et al. (2005) (-)
Gale et al. (2013) (+)	Bipolar Disorder	Gildengers et al. (2009) (-)
Gale et al. (2008) (-)	Major Depressive Disorder	Wilson et al. (2014) (-)
Dickson et al. (2012) (-)	Schizophrenia	Hedman et al. (2013) (-)
Brain measures		
Aribisala et al. (2014) (+)	Hippocampal Volume	van Petten et al. (2004)
Royle et al. (2013) (+)	Intracranial Volume	Pietschnig et al. (2014) (+)
N/A	Infant Head Circumference	Gale et al. (2003) (+)
Physical and physiological measures		
Starr et al. (2004) (-)	Blood Pressure: Diastolic	Taylor et al. (2013) (+/-) Novak & Hajjar (2010) (+/-)
		Gottesman et al. (2014) (-) Novak & Hajjar (2010) (+/-)
Belsky et al. (2013) (-)	BMI	Dahl et al. (2010) (-)
No reference found.	Height	Russ et al. (2014) (+)
Calvin et al. (2011) (+)	Longevity	N/A
Richards et al. (2005) (+)	Forced Expiratory Volume in 1s	Emery et al. (2012) (+)
Life-course Cognitive traits and proxies		
N/A	Childhood cognitive ability	Deary et al. (2013) (+)
Strenze (2007) (+)	College degree	Clouston et al. (2012) (+)
Strenze (2007) (+)	Years of Education	Banks & Mazzonna (2012) (+)

References for Supplementary Table 1

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Descriptions of Cognitive Phenotypes

Reaction Time Test

Reaction Time (RT) was measured in all participants using a computer-based ‘Snap’ game, conceptually similar to some ‘Go/No-Go’ reaction time tasks. Two cards with simple symbols (e.g. a square or equals sign), were presented to participants on a computer screen. Participants were instructed to push an adjacent button box as quickly as possible, using their dominant hand, if the two cards had identical symbols. After completing four practice trials, participants completed eight experimental trials, of which four included identical pairs; these four required a button to be pressed. Each participant’s RT score was calculated as the mean time (in ms) to push the button for the four trials in which the stimuli were identical. Owing to a positively-skewed distribution, the reaction time data were log-transformed before analysis. One participant with an outlying reaction time score (1905 ms, which is over 11 standard deviations above the mean RT) had their data removed from the analysis. The Cronbach alpha coefficient, which provides an internal consistency type of reliability, for the five trials was 0.85. The UK Biobank Field IDs used in this test were 401, 402, 403, and 404. There is a linear decline in mean performance (with longer reaction times found) between age 40 and 70 years (Supplementary Figure 1, below).

Memory (Pairs Matching) Test

Memory was measured using a computerised ‘pairs matching’ game. There were two rounds of the game. In the first round, three pairs of cards with matching simple symbols, arranged randomly in a grid, were presented to participants on a computer screen for three seconds. The cards were then ‘turned’ face down. The participants were instructed to select, from recall and in the fewest number of attempts, the pairs of cards that had matching symbols. Pairs were identified by the participant’s touching identical cards on the screen consecutively. There was no time limit and the participants could make as many attempts as they needed to find all the pairs. The second round included six pairs of cards, shown for five seconds. Only the results from this second, more challenging round of the memory test were used in this study. The memory test score in the present study is the total number of errors made during this task until the six pairs of identical cards were touched consecutively. Twenty-nine participants who made more than 30 errors on the task had their number of errors set to 30 (this was not performed for the GWAS analysis, therefore this does not apply to the LD regression analysis). The UK Biobank field ID for the variable used here (number of errors in the second round) was 399. There is a linear decline in mean performance (more errors) between age 40 and 70 years (Supplementary Figure 1, below).

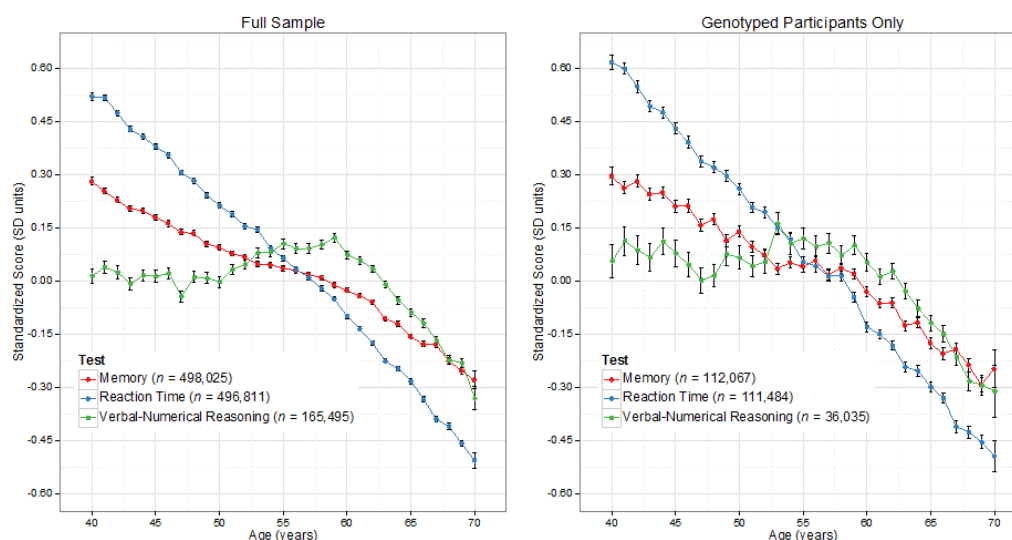
Verbal-numerical Reasoning Test

This test is named ‘fluid intelligence’ in UK Biobank. This verbal-numerical reasoning test comprised thirteen questions presented serially on a computer screen. There were six verbal items. There were seven numerical items, involving sequence recognition and arithmetic. Participants were required to answer all the items within two minutes. All were multiple-choice. An example verbal item is: “Age is to years as height is to?” (answer options were, “Long/Deep/Top/Metres/Tall/Do not know/Prefer not to answer”). An example numerical item is: “150...137...125...114...104... what comes next?” (answer options were, “96/95/94/93/92/Do not know/Prefer not to answer”). The total score out of thirteen was recorded and used for the present study. The Cronbach alpha coefficient for the thirteen

items was 0.62. The UK Biobank Field IDs (variable names) used in this test, with each one corresponding to each of the 13 items, were 4935, 4946, 4957, 4968, 4979, 4990, 5001, 5012, 5556, 5699, 5779, 5790, and 5866. The scores on this test show stable mean values between age 40 and 60 years, and linear decline in mean scores between age 60 and 70 years (Supplementary Figure 1, below). Therefore, this test does not, across the whole age range, show the characteristic age-related decline expected from ‘fluid’ cognitive functions—the name the test has in UK Biobank—and so we refer to the test by its content, which is verbal-numerical reasoning. The cross-sectional age-related pattern of this test is similar to that shown by vocabulary tests, which are used to assess crystallised cognitive ability (Salthouse TA, Localizing age-related individual differences in a hierarchical structure. Intelligence; 32, 541-561, Figure 3).

Educational Attainment

As part of the sociodemographic questionnaire in the study, participants were asked, “Which of the following qualifications do you have? (You can select more than one)”. Possible answers were: “College or University Degree/A levels or AS levels or equivalent/O levels or GCSE or equivalent/CSEs or equivalent/NVQ or HND or HNC or equivalent/Other professional qualifications e.g. nursing, teaching/None of the above/Prefer not to answer”. For the present study, a binary education variable was created to indicate whether or not a participant had a college or university-level degree. This educational attainment variable was used in this study as what has been named and validated as a ‘proxy phenotype’ for cognitive function (Rietveld CA, Esko T, Davies G, et al. Common genetic variants associated with cognitive performance identified using the proxy-phenotype method. Proc Natl Acad Sci 2014; 111: 13790-13794).



Supplementary Figure 1. Age trends in standardized mean scores for the three cognitive abilities (Memory, Reaction Time, and Verbal-Numerical Reasoning) in the full sample (left) and the participants with genotyping data available (right). Error bars represent +/- one standard error of the mean. Valid sample sizes are shown for each individual test. Memory and Reaction Time tests had scores reversed so that lower scores indicate poorer performance for all three tests. For the ‘Full Sample’ figure, six participants aged under 40 years and seven participants aged over 70 years were removed. For the ‘Genotyped Participants Only’ figure, one participant aged over 70 years was removed.

Genotyping and Quality Control

Genotyping was performed on 33 batches of ~4700 samples by Affymetrix, who also performed initial quality control of the genotyping data. Further details are available of the sample processing specific to the UK Biobank project (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583>) and the Axiom array (http://media.affymetrix.com/support/downloads/manuals/axiom_2_assay_auto_workflow_user_guide

.pdf). Prior to the release of the UK Biobank genetic data a stringent QC protocol was applied, and performed at the Wellcome Trust Centre for Human Genetics (WTCHG); details of this process can be found at the following URL (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580>). Prior to the analyses described in the main report, further quality control measures were applied by the present authors. Individuals were removed based on missingness, relatedness (KING estimated kinship coefficient > 0.0442), gender mismatch, non-British ancestry (principal component analysis identified probable Caucasians within those individuals that were self-identified as British), and QC failure in the UK BiLeve study. A sample of 112 151 individuals remained for further analyses. A minor allele frequency of maf < 1% filter was applied and only autosomal variants were used in this study (N = 705 516).

Genome-wide association analyses (GWAS) in the UK Biobank sample

An imputed dataset, including >70 million variants, was made available in which the UK Biobank interim release was imputed to a reference set which combined the UK10K haplotype and 1000 Genomes Phase 3 reference panels. Further details can be found at the following URL: <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020>. Genome-wide association analyses were performed on the imputed dataset using SNPTEST v2.5.1 (Marchini J, Howie B, Myers S, et al. A new multipoint method for genome-wide association studies via imputation of genotypes. *Nat Genet* 2007; 39: 906-913; SNPTEST v.2.5.1 can be found at the following URL: https://mathgen.stats.ox.ac.uk/genetics_software/snpctest/snpctest.html#introduction). An additive model was specified using the "frequentist 1" option. To account for genotype uncertainty we analysed the expected genotyped counts (dosages). Adjustments for age, sex, genotyping batch, genotyping array, assessment centre and 10 principal components were included. Prior to use in LD regression analyses the association results were filtered based on minor allele frequency (<0.1%) and imputation quality (<0.1).

Sources of genetic results from genome-wide association consortia

CARDIoGRAM

Coronary artery disease data have been contributed by CARDIoGRAMplusC4D investigators.

CHARGE-Aging and Longevity

Longevity data have been provided by the CHARGE-Aging and Longevity consortium. Longevity was defined as reaching age 90 years or older. Genotyped participants who died between the ages of 55 and 80 years were used as the control group. There were 6036 participants who achieved longevity and 3757 participants in the control group across participating studies in the discovery meta-analysis.

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Acknowledgments

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DIAGRAM

Type 2 diabetes data were obtained from the DIAGRAM consortium.

International Consortium of Blood Pressure (ICBP)

Blood pressure data were provided by ICBP.

Early Growth Genetics Consortium (EGG)

Head circumference data has been contributed by the EGG Consortium.

ENIGMA

Brain imaging data were obtained from the ENIGMA consortium.

GIANT

Height and BMI data were obtained from the GIANT consortium.

International Genomics of Alzheimer's Project (IGAP)

Alzheimer's disease data were obtained from (IGAP)

Material and methods

International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7 055 881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17 008 Alzheimer's disease cases and 37 154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11 632 SNPs were genotyped and tested for association in an independent set of 8572 Alzheimer's disease cases and 11 312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.

Acknowledgments

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METASTROKE

Ischaemic stroke data were obtained from the METASTROKE consortium. The METASTROKE consortium is supported by NINDS (NS017950). We thank all study participants, volunteers, and study personnel that made this consortium possible. The METASTROKE study consists of combined data from 15 GWAS of IS (12 389 cases vs 62 004 controls). We used TOAST criteria¹⁷ to classify IS as large artery stroke (LAS) (2167 cases/49 159 controls from 11 studies), cardioembolic stroke (CE) (2365 cases/ 56,140 controls from 13 studies), and small vessel disease (SVD) (1894 cases/51 976 controls from 12 studies). METASTROKE studies consisted of independently performed genome-wide single nucleotide polymorphism (SNP) genotyping using standard technologies and imputation to HapMap release 21 or 22 CEU phased genotype¹⁸ or 1000 Genome reference panels. Investigators contributed summary statistical data from association analyses using frequentist additive models for metaanalysis after application of appropriate quality control measures. Polygenic scores reveal combined effects of multiple nonsignificant variants derived from a derivation sample and tested in an independent replication sample. We derived polygenic scores for multiple p value cutoffs (0.5, 0.25, 0.1, 0.05, 0.01, 0.001, and 0.0001) in derivation samples.

Psychiatric Genetics Consortium

Schizophrenia, bipolar disorder, major depressive disorder, ADHD and autism data were obtained from the Psychiatric Genetics Consortium.

Social Science Genetic Association Consortium

Years of education, college degree and childhood cognitive ability data were obtained from the Social Science Genetic Association Consortium.

SpiroMeta/CHARGE-Pulmonary

Lung function data were obtained from the SpiroMeta and CHARGE-Pulmonary consortia.

Supplementary Table 2

Sources of genetic results from genome-wide association consortia.

Pheno type	Consortium	URL	Reference	No. of individuals in GWAS
Coronary Artery Disease	CARDIoGRAM	http://www.cardiogramplusc4d.org/downloads/	Schunkert et al. Nat Genet 2011; 43: 333-338. PMID: 21378990	22 233 cases 64 762 controls
Stroke: Ischaemic	METASTROKE	http://www.strokegenetics.com/members-area/meta-stroke	Traylor et al. Lancet Neurol 2012; 11: 951-962. PMID: 23041239	12 389 cases 62,004 controls
Stroke: Cardioembolic	METASTROKE	http://www.strokegenetics.com/members-area/meta-stroke	Traylor et al. Lancet Neurol 2012; 11: 951-962. PMID: 23041239	2365 cases 62 004 controls
Stroke: Large-vessel disease	METASTROKE	http://www.strokegenetics.com/members-area/meta-stroke	Traylor et al. Lancet Neurol 2012; 11: 951-962. PMID: 23041239	2167 cases 62 004 controls
Stroke: Small-vessel disease	METASTROKE	http://www.strokegenetics.com/members-area/meta-stroke	Traylor et al. Lancet Neurol 2012; 11: 951-962. PMID: 23041239	1894 cases 62 004 controls
Type 2 diabetes	DIAGRAM	http://diagram-consortium.org/downloads.html	Morris et al. Nat Genet 2012; 44: 981-990. PMID: 22885922	12 171 cases 56 862 controls
ADHD	Psychiatric Genetics Consortium (PGC)	https://www.med.un.c.edu/pgc/downloads	Cross-Disorder Group of the Psychiatric Genomics Consortium. Lancet 2013; 381: 1371-1379. PMID: 23453885	1947 trio cases 1947 trio pseudocontrols, 840 cases 688 controls
Alzheimer's disease	International Genomics of Alzheimer's Project (IGAP)	http://www.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php	Lambert et al. Nat Genet 2013; 45: 1452-1458. PMID: 24162737	17 008 cases 37 154 controls
Autism	Psychiatric Genetics Consortium (PGC)	https://www.med.un.c.edu/pgc/downloads	Cross-Disorder Group of the Psychiatric Genomics Consortium. Nat Genet 2013; 45: 984-994. PMID: 23933821	3303 cases 3428 controls
Bipolar disorder	Psychiatric Genetics Consortium (PGC)	https://www.med.un.c.edu/pgc/downloads	Psychiatric GWAS Consortium Bipolar Disorder Working Group. Nat Genet 2011; 43: 977-983. PMID: 21926972	7481 cases 9250 controls
Major depressive disorder	Psychiatric Genetics Consortium (PGC)	https://www.med.un.c.edu/pgc/downloads	Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. Mol Psychiatry 2013; 18: 497-511. PMID: 22472876	9240 cases 9519 controls
Schizophrenia	Psychiatric Genetics Consortium (PGC)	https://www.med.un.c.edu/pgc/downloads	Schizophrenia Working Group of the Psychiatric Genomics Consortium. Nature 2014; 511: 421-427. PMID: 25056061	36 989 cases 113 075 controls
Hippocampal volume	ENIGMA	http://enigma.ini.usc.edu/ongoing/gwasm-a-of-subcorticalstructures/	Hibar et al. Nature 2015; 520: 224-229. PMID: 25607358	13 171
Intracranial volume	ENIGMA	http://enigma.ini.usc.edu/ongoing/gwasm-a-of-subcorticalstructures/	Hibar et al. Nature 2015; 520: 224-229. PMID: 25607358	13 171
BMI	GIANT	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Locke et al. Nature 2015; 518: 197-206. PMID: 25673413	339 224

Diastolic blood pressure	International Consortium of Blood Pressure (ICBP)		Ehret et al. (2011) Nature 478, 103-109. PMID: 21909115	69 395
Height	GIANT	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Wood et al. Nat Genet 2014; 11: 1173-86. PMID: 25282103	253 288
Infant head circumference	Early Growth Genetics Consortium	http://egg-consortium.org/head-circumference.html	Taal et al. Nat Genet 2012; 15: 532-538. PMID: 22504419	10 768
Longevity	CHARGE-Aging and Longevity		Broer et al. J Gerontol A Biol Sci Med Sci 2015; 70: 110-118. PMID: 25199915	603 6 case s 375 7 cont rols 48 201
Forced expiratory volume in 1 second (FEV1)	SpiroMeta/CHARGE-Pulmonary		Soler Artigas et al. Nature Genetics 2011; 43: 1082-1090. PMID: 21946350	69 395
Systolic blood pressure	International Consortium of Blood Pressure (ICBP)		Ehret et al. Nature 2011; 478: 103-109. PMID: 21909115	69 395
Childhood cognitive ability	Social Science Genetic Association Consortium	http://ssgac.org/Data.php	Benyamin et al. Mol Psychiatry 2014; 19: 253-258. PMID: 23358156	17 989
College degree	Social Science Genetic Association Consortium	http://ssgac.org/Data.php	Rietveld et al. Science 2013; 314: 1467-1471. PMID: 23722424	95 427
Years of Education	Social Science Genetic Association Consortium	http://ssgac.org/Data.php	Rietveld et al. Science 2013; 314: 1467-1471. PMID: 23722424	101 069

LD regression genetic correlation procedure

The patterns of LD found across the genome enable genetic correlations between traits to be derived. This is due to two reasons. Firstly, the level of association a SNP shows in a GWAS is a product of both its own contribution toward a phenotype and those that are in LD with it (Yang J, Weedon MN, Purcell S, et al. Genomic inflation factors under polygenic inheritance. *Eur J Hum Genet* 2011;19: 807-812). Additionally, SNPs in regions of high LD tag a greater proportion of the genome than SNPs in regions of low LD. These two facts mean that, assuming a polygenic architecture, SNPs in regions of high LD will have greater association statistics than SNPs found in regions of low LD. The effect of this is that GWAS association test statistics can be predicted using LD (Bulik-Sullivan B, Finucane HK, Anttila V et al. An atlas of genetic correlations across human diseases and traits. *bioRxiv* 2015; doi: <http://dx.doi.org/10.1101/014498>). This logic can also be extended to a bivariate design, where LD can be used to predict the product of pairs of test statistics for each locus across GWAS datasets (Bulik-Sullivan B, Loh PR, Finucane H, et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 2015; 47: 291-295).

We followed the protocol of the above studies by Bulik-Sullivan et al., where data sets demonstrating a heritability Z-score (h^2_z) > 4 and a mean χ^2 statistic of > 1.02 were included. All traits, except small vessel disease exceeded these thresholds. This threshold was implemented in order to establish that each GWAS data set had evidence of a clear polygenic signal. Where it was included in the summary statistics provided, a MAF of > 0.01 was used as a cut off. To control for imputation quality, only those SNPs found in the HapMap3 with 1000 Genomes EUR with a MAF > 0.05 were included (integrated_phase1_v3.20101123). Next, indels and structural variants were removed along with strand-ambiguous SNPs. Finally, genome-wide significant SNPs were removed, as were SNPs with very large effect sizes ($\chi^2 > 80$), as the presence of outliers can increase the standard error in a regression model. LD scores and weights for use with the GWAS of European ancestry were downloaded from the Broad institute (http://www.broadinstitute.org/~bulik/eur_ldscores/). An unconstrained intercept was used in the regression model as it was not possible to quantify the degree of sample overlap between the traits used here.

Polygenic profiling procedure

The genetic data files (.map and .ped files) supplied from Biota (the UK Biobank online repository) were unsuitable for use in the polygenic profile analyses as the .ped allele coding used a 1, 2 numeric allele encode rather than the standard ACGT encode format. In order to enable the analysis, the .ped files were recoded to the standard encode format. To achieve this, a bespoke programme was developed to create new files using a lookup-substitution method. A fast-in-memory lookup string hash table was created to hold the SNP-ID, along with the allele identifiers for the SNP. A simple loop then performed serialised lookups based on string position, to create an associated string with the correct ACGT encode. This was then appended to the six mandatory data fields extracted from initial string. In order to maximise performance and enable timely completion of the lookup-substitution, these loops were run in parallel threads in a standard multiprocessor environment.

Sensitivity analysis

To test whether FDR significant associations between polygenic risk for coronary artery disease, and Verbal-numerical reasoning and educational attainment were confounded by individuals diagnosed with cardiovascular disease, 2779 individuals who had had a heart attack and 2521 individuals with angina were removed from the regression analysis. Similarly 5800 individuals with diabetes (type 1 or type 2) were removed from the regression investigating an association between polygenic risk for type 2 diabetes and educational attainment. Finally, 26 912 individuals with hypertension were removed from the regression analysis investigating the association between polygenic risk for systolic blood pressure and educational attainment.

Supplementary Table 3

Number of SNPs included at each threshold for the polygenic profile scores.

		Threshold	Number of SNPs
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	2633
		0.05	9981
		0.1	18159
		0.5	72443
		1	121718
	Stroke: Ischaemic	0.01	3006
		0.05	13448
		0.1	25588
		0.5	105309
		1	173745
	Stroke: Cardioembolic	0.01	2885
		0.05	13295
		0.1	25366
		0.5	104731
		1	172809
	Stroke: Large Vessel Disease	0.01	2915
		0.05	13354
		0.1	25243
		0.5	104188
		1	172973
	Stroke: Small Vessel Disease	0.01	2853
		0.05	13116
		0.1	25303
		0.5	104042
		1	172697

Neuro-Psychiatric Disorders	Type 2 Diabetes	0.01	2461
		0.05	9969
		0.1	18172
		0.5	73505
		1	124964
	ADHD	0.01	1394
		0.05	6357
		0.1	12305
		0.5	55047
		1	98438
	Alzheimer's Disease	0.01	5030
		0.05	20437
		0.1	37843
		0.5	152714
		1	254358
	Autism	0.01	4736
		0.05	22299
		0.1	43182
		0.5	192694
		1	334262
	Bipolar Disorder	0.01	2625
		0.05	10418
		0.1	18907
		0.5	75289
		1	127481
	Major Depressive Disorder	0.01	1532
		0.05	6878
		0.1	12995
		0.5	56175
		1	98450
	Schizophrenia	0.01	12006
		0.05	35598
		0.1	58837
		0.5	194510
		1	310629
Brain Measures	Hippocampal Volume	0.01	3954
		0.05	17974
		0.1	34469
		0.5	148964
		1	252716
	Intracranial Volume	0.01	4046
		0.05	18683
		0.1	35510
		0.5	150389
		1	253355
	Infant Head Circumference	0.01	2031
		0.05	9004

Physical and physiological measures	Blood Pressure: Diastolic	0.1	16994
		0.5	73859
		1	127665
		0.01	1952
		0.05	8535
	Blood Pressure: Systolic	0.1	16298
		0.5	74773
		1	133754
		0.01	1961
		0.05	8379
	BMI	0.1	16253
		0.5	74616
		1	133823
		0.01	2612
		0.05	8503
	Height	0.1	15648
		0.5	72010
		1	131142
		0.01	11360
		0.05	23651
	Longevity	0.1	34188
		0.5	86984
		1	131070
		0.01	2023
		0.05	9292
Life-course Cognitive Traits and Proxies	Forced Expiratory Volume in 1s (FEV ₁)	0.1	17646
		0.5	77146
		1	133920
		0.01	1963
		0.05	8677
	Childhood Cognitive Ability	0.1	16794
		0.5	76920
		1	136779
		0.01	1187
		0.05	4945
	College degree	0.1	9069
		0.5	37967
		1	65356
		0.01	2715
		0.05	10076
	Years of Education	0.1	17650
		0.5	66808
		1	109983
		0.01	2702
		0.05	9886
		0.1	17577
		0.5	65990

Life-course Cognitive Traits and Proxies	Years of Education	1	108127
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Supplementary Table 4a

Associations between polygenic profiles of health-related traits, and verbal-numerical reasoning controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values ($P < 0.0188$) are shown in bold. Cognitive/education phenotypes are scored such that higher scores indicate better performance.

Trait category	Trait	Verbal-Numerical Reasoning				
		Threshold	β	SE	R2	P
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	-0.017	0.0052	0.0003	0.0009
		0.05	-0.012	0.0052	0.0002	0.0188
		0.1	-0.011	0.0052	0.0001	0.0393
		0.5	-0.019	0.0052	0.0004	0.0002
		1	-0.018	0.0052	0.0003	0.0005
	Stroke: Ischaemic	0.01	-0.010	0.0053	0.0001	0.0474
		0.05	-0.014	0.0053	0.0002	0.0068
		0.1	-0.006	0.0053	3.47×10^{-5}	0.2604
		0.5	-0.007	0.0053	4.42×10^{-5}	0.2041
		1	-0.003	0.0053	1.02×10^{-5}	0.5428
	Stroke: Cardioembolic	0.01	0.005	0.0052	2.45×10^{-5}	0.3444
		0.05	0.000	0.0052	8.40×10^{-8}	0.9558
		0.1	-0.005	0.0052	2.06×10^{-5}	0.3858
		0.5	-0.008	0.0052	0.0001	0.1092
		1	-0.009	0.0052	0.0001	0.0937
	Stroke: Large Vessel Disease	0.01	-0.013	0.0053	0.0002	0.0155
		0.05	-0.004	0.0053	1.28×10^{-5}	0.4948
		0.1	-0.007	0.0053	4.24×10^{-5}	0.2134
		0.5	-0.002	0.0052	4.11×10^{-6}	0.6986
		1	-0.010	0.0052	0.0001	0.0629
	Stroke: Small Vessel Disease	0.01	-0.005	0.0052	2.99×10^{-5}	0.2962
		0.05	-0.012	0.0053	0.0001	0.0250
		0.1	-0.007	0.0053	4.34×10^{-5}	0.2085
		0.5	0.001	0.0052	8.21×10^{-7}	0.8626
		1	0.001	0.0052	1.26×10^{-6}	0.8300
	Type 2 Diabetes	0.01	-0.002	0.0053	5.84×10^{-6}	0.6446
		0.05	-0.001	0.0053	1.63×10^{-6}	0.8073
		0.1	-0.004	0.0053	1.60×10^{-5}	0.4442
		0.5	-0.006	0.0054	2.98×10^{-5}	0.2969
		1	-0.006	0.0054	3.64×10^{-5}	0.2490
Neuro-Psychiatric Disorders	ADHD	0.01	-0.002	0.0052	5.74×10^{-6}	0.6474
		0.05	-0.001	0.0052	3.12×10^{-7}	0.9150
		0.1	-0.004	0.0052	1.67×10^{-5}	0.4354
		0.5	-0.007	0.0052	0.0001	0.1597
		1	-0.008	0.0052	0.0001	0.1054
	Alzheimer's Disease	0.01	-0.014	0.0052	0.0002	0.0061
		0.05	-0.023	0.0053	0.0005	1.27×10^{-5}
		0.1	-0.023	0.0053	0.0005	1.34×10^{-5}
		0.5	-0.021	0.0053	0.0004	0.0001
		1	-0.022	0.0053	0.0005	3.97×10^{-5}
	Autism	0.01	0.016	0.0052	0.0003	0.0023

Brain Measures		0.05	0.016	0.0052	0.0002	0.0028
		0.1	0.019	0.0052	0.0003	0.0004
		0.5	0.022	0.0052	0.0005	1.92×10⁻⁵
		1	0.023	0.0052	0.0005	1.43×10⁻⁵
	Bipolar Disorder	0.01	−0.006	0.0052	3.34×10 ⁻⁵	0.2695
		0.05	−0.003	0.0053	7.87×10 ⁻⁶	0.5920
		0.1	−0.003	0.0053	1.01×10 ⁻⁵	0.5433
		0.5	−0.004	0.0053	1.24×10 ⁻⁵	0.5006
		1	−0.004	0.0053	1.59×10 ⁻⁵	0.4463
	Major Depressive Disorder	0.01	−0.008	0.0053	0.0001	0.1455
		0.05	−0.008	0.0053	0.0001	0.1366
		0.1	−0.014	0.0053	0.0002	0.0071
		0.5	−0.018	0.0053	0.0003	0.0005
		1	−0.020	0.0053	0.0004	0.0002
	Schizophrenia	0.01	−0.055	0.0053	0.0030	2.04×10⁻²⁵
		0.05	−0.062	0.0053	0.0038	7.73×10⁻³²
		0.1	−0.062	0.0053	0.0037	3.22×10⁻³¹
		0.5	−0.062	0.0054	0.0037	2.59×10⁻³¹
		1	−0.062	0.0054	0.0036	1.34×10⁻³⁰
	Hippocampal Volume	0.01	0.005	0.0052	2.34×10 ⁻⁵	0.3552
		0.05	0.000	0.0052	1.05×10 ⁻⁸	0.9844
		0.1	−0.002	0.0052	4.24×10 ⁻⁶	0.6943
		0.5	0.002	0.0052	2.78×10 ⁻⁶	0.7500
		1	−0.001	0.0052	3.26×10 ⁻⁷	0.9132
	Intracranial Volume	0.01	0.013	0.0053	0.0002	0.0113
		0.05	0.009	0.0053	0.0001	0.0895
		0.1	0.013	0.0053	0.0002	0.0140
		0.5	0.016	0.0054	0.0003	0.0021
		1	0.016	0.0054	0.0003	0.0023
	Infant Head Circumference	0.01	0.019	0.0052	0.0003	0.0004
		0.05	0.019	0.0053	0.0003	0.0004
		0.1	0.020	0.0053	0.0004	0.0002
		0.5	0.024	0.0053	0.0005	8.53×10⁻⁶
		1	0.023	0.0053	0.0005	1.51×10⁻⁵
Physical and physiological measures	Blood Pressure: Diastolic	0.01	0.001	0.0052	1.53×10 ⁻⁶	0.8132
		0.05	0.004	0.0052	1.22×10 ⁻⁵	0.5044
		0.1	0.000	0.0053	6.52×10 ⁻⁸	0.9611
		0.5	0.003	0.0053	7.91×10 ⁻⁶	0.5911
		1	0.003	0.0053	9.49×10 ⁻⁶	0.5563
	Blood Pressure: Systolic	0.01	0.008	0.0052	0.0001	0.1138
		0.05	0.008	0.0052	0.0001	0.1324
		0.1	0.013	0.0052	0.0002	0.0116
		0.5	0.007	0.0053	0.0001	0.1582
		1	0.008	0.0053	0.0001	0.1211
	BMI	0.01	−0.022	0.0052	0.0005	2.92×10⁻⁵
		0.05	−0.024	0.0052	0.0006	3.44×10⁻⁶
		0.1	−0.024	0.0052	0.0006	6.49×10⁻⁶

Life-course Cognitive Traits and Proxies	Height		0.5	-0.027	0.0052	0.0007	3.34×10⁻⁷
			1	-0.026	0.0052	0.0007	8.52×10⁻⁷
			0.01	0.017	0.0053	0.0003	0.0011
			0.05	0.019	0.0053	0.0004	0.0003
			0.1	0.019	0.0054	0.0003	0.0004
	Longevity		0.5	0.021	0.0054	0.0004	0.0001
			1	0.021	0.0054	0.0004	0.0001
			0.01	0.004	0.0053	1.87×10 ⁻⁵	0.4091
			0.05	0.000	0.0053	4.62×10 ⁻⁸	0.9673
			0.1	0.000	0.0052	7.30×10 ⁻⁸	0.9588
	Forced Expiratory Volume in 1s (FEV ₁)		0.5	0.000	0.0052	1.31×10 ⁻⁷	0.9449
			1	0.000	0.0052	1.98×10 ⁻⁸	0.9786
			0.01	0.000	0.0052	2.08×10 ⁻⁷	0.9306
			0.05	0.007	0.0052	0.0001	0.1604
			0.1	0.007	0.0052	4.38×10 ⁻⁵	0.2064
	Childhood Cognitive Ability		0.5	0.012	0.0052	0.0001	0.0220
			1	0.011	0.0052	0.0001	0.0319
			0.01	0.031	0.0052	0.0010	3.12×10⁻⁹
			0.05	0.052	0.0052	0.0027	2.55×10⁻²³
			0.1	0.063	0.0052	0.0040	1.45×10⁻³³
	College degree		0.5	0.077	0.0052	0.0059	1.70×10⁻⁴⁸
			1	0.079	0.0052	0.0062	3.49×10⁻⁵¹
			0.01	0.069	0.0052	0.0048	3.92×10⁻⁴⁰
			0.05	0.085	0.0052	0.0071	1.05×10⁻⁵⁸
			0.1	0.095	0.0052	0.0089	5.93×10⁻⁷³
	Years of Education		0.5	0.102	0.0052	0.0102	3.19×10⁻⁸³
			1	0.101	0.0052	0.0101	2.56×10⁻⁸²
			0.01	0.077	0.0052	0.0058	1.88×10⁻⁴⁸
			0.05	0.090	0.0052	0.0080	2.26×10⁻⁶⁵
			0.1	0.096	0.0052	0.0091	7.36×10⁻⁷⁵
			0.5	0.105	0.0053	0.0109	6.20×10⁻⁸⁹
			1	0.106	0.0053	0.0109	2.96×10⁻⁸⁹

Supplementary Table 4b

Associations between polygenic profiles of health related traits and Reaction Time (log transformed) controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values ($P < 0.0188$) are shown in bold. Cognitive/education phenotypes are scored such that higher scores indicate better performance.

Trait category	Trait	Reaction Time				
		Threshold	β	SE	R2	p
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	3.24×10^{-5}	0.0005	3.03×10^{-8}	0.9508
		0.05	2.80×10^{-4}	0.0005	2.27×10^{-6}	0.5939
		0.1	0.001	0.0005	2.33×10^{-5}	0.0875
		0.5	0.001	0.0005	1.37×10^{-5}	0.1894
		1	0.001	0.0005	1.83×10^{-5}	0.1301
	Stroke: Ischaemic	0.01	-0.001	0.0005	2.46×10^{-5}	0.0791
		0.05	-3.00×10^{-4}	0.0005	2.53×10^{-6}	0.5735
		0.1	2.52×10^{-4}	0.0005	1.76×10^{-6}	0.6385
		0.5	-3.68×10^{-5}	0.0005	3.73×10^{-8}	0.9455
		1	-1.53×10^{-4}	0.0005	6.58×10^{-7}	0.7740
	Stroke: Cardioembolic	0.01	0.001	0.0005	2.42×10^{-5}	0.0817
		0.05	0.001	0.0005	1.47×10^{-5}	0.1746
		0.1	0.001	0.0005	7.98×10^{-6}	0.3175
		0.5	1.74×10^{-4}	0.0005	8.71×10^{-7}	0.7412
		1	-2.32×10^{-5}	0.0005	1.55×10^{-8}	0.9648
	Stroke: Large Vessel Disease	0.01	5.86×10^{-5}	0.0005	9.86×10^{-8}	0.9115
		0.05	2.26×10^{-4}	0.0005	1.44×10^{-6}	0.6714
		0.1	-1.54×10^{-4}	0.0005	6.66×10^{-7}	0.7726
		0.5	4.45×10^{-6}	0.0005	5.72×10^{-10}	0.9932
		1	-2.03×10^{-4}	0.0005	1.19×10^{-6}	0.6991
	Stroke: Small Vessel Disease	0.01	-3.12×10^{-4}	0.0005	2.82×10^{-6}	0.5525
		0.05	1.05×10^{-4}	0.0005	3.16×10^{-7}	0.8424
		0.1	-1.45×10^{-4}	0.0005	6.04×10^{-7}	0.7832
		0.5	-4.53×10^{-4}	0.0005	5.94×10^{-6}	0.3882
		1	-0.001	0.0005	7.93×10^{-6}	0.3188
	Type 2 Diabetes	0.01	-4.33×10^{-4}	0.0005	5.36×10^{-6}	0.4124
		0.05	-3.10×10^{-4}	0.0005	2.71×10^{-6}	0.5602
		0.1	-4.50×10^{-4}	0.0005	5.70×10^{-6}	0.3982
		0.5	-3.65×10^{-5}	0.0005	3.67×10^{-8}	0.9459
		1	-8.44×10^{-5}	0.0005	1.96×10^{-7}	0.8755
Neuro-Psychiatric Disorders	ADHD	0.01	-2.71×10^{-4}	0.0005	2.13×10^{-6}	0.6053
		0.05	6.76×10^{-5}	0.0005	1.32×10^{-7}	0.8976
		0.1	4.14×10^{-5}	0.0005	4.97×10^{-8}	0.9371
		0.5	-0.001	0.0005	8.45×10^{-6}	0.3036
		1	-0.001	0.0005	1.06×10^{-5}	0.2485
	Alzheimer's Disease	0.01	-4.31×10^{-4}	0.0005	5.38×10^{-6}	0.4116
		0.05	-0.001	0.0005	2.04×10^{-5}	0.1096
		0.1	-2.30×10^{-4}	0.0005	1.53×10^{-6}	0.6619
		0.5	-0.001	0.0005	3.02×10^{-5}	0.0516
		1	-0.001	0.0005	2.64×10^{-5}	0.0692

Brain Measures	Autism	0.01	0.001	0.0005	1.78×10^{-5}	0.1348
		0.05	0.001	0.0005	1.24×10^{-5}	0.2124
		0.1	0.001	0.0005	1.95×10^{-5}	0.1176
		0.5	0.001	0.0005	1.01×10^{-5}	0.2612
		1	0.001	0.0005	1.01×10^{-5}	0.2605
	Bipolar Disorder	0.01	-0.002	0.0005	9.08×10^{-5}	0.0007
		0.05	-0.002	0.0005	7.79×10^{-5}	0.0018
		0.1	-0.002	0.0005	8.68×10^{-5}	0.0010
		0.5	-0.002	0.0005	8.54×10^{-5}	0.0011
		1	-0.002	0.0005	8.98×10^{-5}	0.0008
	Major Depressive Disorder	0.01	-0.001	0.0005	2.95×10^{-5}	0.0544
		0.05	-0.002	0.0005	7.22×10^{-5}	0.0026
		0.1	-0.002	0.0005	9.61×10^{-5}	0.0005
		0.5	-0.002	0.0005	8.30×10^{-5}	0.0013
		1	-0.002	0.0005	6.50×10^{-5}	0.0043
	Schizophrenia	0.01	-0.005	0.0005	0.0007	4.24×10^{-22}
		0.05	-0.005	0.0005	0.0008	1.03×10^{-23}
		0.1	-0.006	0.0005	0.0009	1.88×10^{-25}
		0.5	-0.005	0.0005	0.0008	7.56×10^{-24}
		1	-0.005	0.0005	0.0008	2.38×10^{-23}
	Hippocampal Volume	0.01	0.001	0.0005	8.02×10^{-6}	0.3163
		0.05	0.001	0.0005	1.47×10^{-5}	0.1744
		0.1	0.001	0.0005	1.68×10^{-5}	0.1465
		0.5	0.001	0.0005	1.99×10^{-5}	0.1144
		1	0.001	0.0005	1.98×10^{-5}	0.1156
	Intracranial Volume	0.01	0.001	0.0005	7.56×10^{-6}	0.3306
		0.05	3.57×10^{-4}	0.0005	3.60×10^{-6}	0.5020
		0.1	3.32×10^{-4}	0.0005	3.08×10^{-6}	0.5346
		0.5	3.29×10^{-4}	0.0005	2.97×10^{-6}	0.5418
		1	3.21×10^{-4}	0.0005	2.83×10^{-6}	0.5514
	Infant Head Circumference	0.01	-0.001	0.0005	3.16×10^{-5}	0.0468
		0.05	-3.01×10^{-4}	0.0005	2.60×10^{-6}	0.5683
		0.1	-1.06×10^{-4}	0.0005	3.20×10^{-7}	0.8413
		0.5	-1.92×10^{-4}	0.0005	1.05×10^{-6}	0.7174
		1	-2.02×10^{-4}	0.0005	1.15×10^{-6}	0.7037
Physical and physiological measures	Blood Pressure: Diastolic	0.01	0.001	0.0005	1.14×10^{-5}	0.2325
		0.05	1.59×10^{-4}	0.0005	7.28×10^{-7}	0.7627
		0.1	3.45×10^{-4}	0.0005	3.43×10^{-6}	0.5120
		0.5	4.50×10^{-4}	0.0005	5.82×10^{-6}	0.3931
		1	0.001	0.0005	7.61×10^{-6}	0.3289
	Blood Pressure: Systolic	0.01	-1.73×10^{-4}	0.0005	8.68×10^{-7}	0.7416
		0.05	-2.58×10^{-4}	0.0005	1.92×10^{-6}	0.6241
		0.1	-4.81×10^{-4}	0.0005	6.66×10^{-6}	0.3609
		0.5	-4.97×10^{-4}	0.0005	7.09×10^{-6}	0.3460
		1	-3.88×10^{-4}	0.0005	4.32×10^{-6}	0.4619
	BMI	0.01	3.96×10^{-4}	0.0005	4.54×10^{-6}	0.4507

Life-course Cognitive Traits and Proxies	Height		0.05	1.99×10^{-5}	0.0005	1.15×10^{-8}	0.9697
			0.1	-4.02×10^{-5}	0.0005	4.67×10^{-8}	0.9390
			0.5	-2.47×10^{-5}	0.0005	1.76×10^{-8}	0.9626
			1	1.79×10^{-5}	0.0005	9.25×10^{-9}	0.9728
			0.01	3.64×10^{-4}	0.0005	3.75×10^{-6}	0.4933
			0.05	2.82×10^{-4}	0.0005	2.21×10^{-6}	0.5985
			0.1	4.06×10^{-4}	0.0005	4.54×10^{-6}	0.4508
			0.5	4.46×10^{-4}	0.0005	5.34×10^{-6}	0.4135
			1	4.07×10^{-4}	0.0005	4.43×10^{-6}	0.4562
		Longevity	0.01	2.47×10^{-5}	0.0005	1.75×10^{-8}	0.9627
	Forced Expiratory Volume in 1s (FEV ₁)		0.05	3.23×10^{-4}	0.0005	2.96×10^{-6}	0.5426
			0.1	1.21×10^{-4}	0.0005	4.25×10^{-7}	0.8176
			0.5	2.30×10^{-4}	0.0005	1.52×10^{-6}	0.6623
			1	1.84×10^{-4}	0.0005	9.73×10^{-7}	0.7270
			0.01	-4.27×10^{-4}	0.0005	5.28×10^{-6}	0.4162
			0.05	-0.001	0.0005	1.83×10^{-5}	0.1302
			0.1	-0.001	0.0005	1.05×10^{-5}	0.2505
			0.5	-2.14×10^{-4}	0.0005	1.33×10^{-6}	0.6836
			1	-2.52×10^{-4}	0.0005	1.84×10^{-6}	0.6310
	Childhood Cognitive Ability		0.01	0.001	0.0005	1.57×10^{-5}	0.1613
			0.05	0.002	0.0005	8.41×10^{-5}	0.0012
			0.1	0.002	0.0005	9.30×10^{-5}	0.0006
			0.5	0.002	0.0005	0.0001	0.0002
			1	0.002	0.0005	8.94×10^{-5}	0.0008
	College Degree		0.01	0.001	0.0005	1.60×10^{-5}	0.1573
			0.05	0.001	0.0005	4.61×10^{-5}	0.0163
			0.1	0.001	0.0005	3.97×10^{-5}	0.0257
			0.5	0.001	0.0005	4.90×10^{-5}	0.0133
			1	0.001	0.0005	4.42×10^{-5}	0.0186
	Years of Education		0.01	0.001	0.0005	2.26×10^{-5}	0.0927
			0.05	0.001	0.0005	2.15×10^{-5}	0.1008
			0.1	0.001	0.0005	4.67×10^{-5}	0.0156
			0.5	0.001	0.0005	2.71×10^{-5}	0.0654
			1	0.001	0.0005	2.92×10^{-5}	0.0558

Supplementary Table 4c

Associations between polygenic profiles of health related traits, and memory controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values ($P < 0.0188$) are shown in bold. Cognitive/education phenotypes are scored such that higher scores indicate better performance.

Trait category	Trait	Memory		SE	R2	p
		Threshold	β			
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	-0.004	0.003	1.27×10^{-5}	0.2265
		0.05	-0.002	0.003	6.08×10^{-6}	0.4036
		0.1	0.000	0.003	2.25×10^{-7}	0.8725
		0.5	0.000	0.003	1.14×10^{-7}	0.9091
		1	0.001	0.003	3.17×10^{-7}	0.8487
	Stroke: Ischaemic	0.01	-0.002	0.0030	3.64×10^{-6}	0.5184
		0.05	-0.001	0.0030	1.04×10^{-7}	0.9128
		0.1	-0.0005	0.0030	4.03×10^{-8}	0.9458
		0.5	-0.004	0.0030	1.60×10^{-5}	0.1759
		1	-0.003	0.0030	1.11×10^{-5}	0.2581
	Stroke: Cardioembolic	0.01	0.004	0.0030	1.62×10^{-5}	0.1721
		0.05	-0.001	0.0030	6.57×10^{-7}	0.7836
		0.1	-0.003	0.0030	1.14×10^{-5}	0.2535
		0.5	0.004	0.0030	1.65×10^{-5}	0.1691
		1	0.005	0.0030	2.99×10^{-5}	0.0638
	Stroke: Large Vessel Disease	0.01	-0.006	0.0030	3.04×10^{-5}	0.0619
		0.05	-0.006	0.0030	3.02×10^{-5}	0.0628
		0.1	-0.008	0.0030	6.69×10^{-5}	0.0056
		0.5	0.0001	0.0030	1.64×10^{-8}	0.9654
		1	-0.001	0.0030	1.39×10^{-6}	0.6892
	Stroke: Small Vessel Disease	0.01	-0.004	0.0030	1.91×10^{-5}	0.1388
		0.05	-0.004	0.0030	1.42×10^{-5}	0.2025
		0.1	-0.002	0.0030	5.97×10^{-6}	0.4080
		0.5	-0.004	0.0030	1.50×10^{-5}	0.1899
		1	-0.003	0.0030	1.15×10^{-5}	0.2512
	Type 2 Diabetes	0.01	0.0003	0.0030	9.07×10^{-8}	0.9187
		0.05	0.002	0.0030	5.23×10^{-6}	0.4387
		0.1	0.0005	0.0030	2.85×10^{-7}	0.8566
		0.5	0.003	0.0030	8.41×10^{-6}	0.3260
		1	0.003	0.0030	1.10×10^{-5}	0.2614
Neuro-Psychiatric Disorders	ADHD	0.01	0.0001	0.0030	9.36×10^{-10}	0.9917
		0.05	-0.001	0.0030	4.39×10^{-7}	0.8224
		0.1	0.001	0.0030	8.42×10^{-7}	0.7560
		0.5	0.001	0.0030	1.77×10^{-6}	0.6520
		1	0.001	0.0030	2.85×10^{-7}	0.8566
	Alzheimer's Disease	0.01	-0.009	0.0030	7.56×10^{-5}	0.0032
		0.05	-0.009	0.0030	7.47×10^{-5}	0.0034
		0.1	-0.011	0.0030	0.000129	0.0001
		0.5	-0.010	0.0030	9.31×10^{-5}	0.0011
		1	-0.009	0.0030	8.87×10^{-5}	0.0014
	Autism	0.01	0.001	0.0030	1.50×10^{-6}	0.6784

Brain Measures		0.05	0.001	0.0030	3.29×10^{-7}	0.8459
		0.1	0.002	0.0030	5.23×10^{-6}	0.4385
		0.5	-0.001	0.0030	2.89×10^{-6}	0.5647
		1	-0.001	0.0030	3.50×10^{-6}	0.5262
	Bipolar Disorder	0.01	-0.012	0.0030	1.45×10^{-4}	4.49×10^{-5}
		0.05	-0.015	0.0030	2.11×10^{-4}	8.77×10^{-7}
		0.1	-0.015	0.0030	2.25×10^{-4}	3.68×10^{-7}
		0.5	-0.017	0.0030	2.66×10^{-4}	3.21×10^{-8}
		1	-0.015	0.0030	2.33×10^{-4}	2.34×10^{-7}
	Major Depressive Disorder	0.01	-0.007	0.0030	5.17×10^{-5}	0.0149
		0.05	-0.006	0.0030	3.91×10^{-5}	0.0342
		0.1	-0.010	0.0030	0.0001	0.0007
		0.5	-0.013	0.0030	0.000174	7.77×10^{-6}
		1	-0.014	0.0030	0.000198	1.91×10^{-6}
	Schizophrenia	0.01	-0.035	0.0030	1.18×10^{-3}	2.73×10^{-31}
		0.05	-0.039	0.0030	1.48×10^{-3}	7.62×10^{-39}
		0.1	-0.039	0.0030	1.49×10^{-3}	4.49×10^{-39}
		0.5	-0.038	0.0030	1.35×10^{-3}	1.65×10^{-35}
		1	-0.037	0.0030	1.30×10^{-3}	2.67×10^{-34}
	Hippocampal Volume	0.01	-0.003	0.0030	7.21×10^{-6}	0.3629
		0.05	-0.003	0.0030	1.07×10^{-5}	0.2674
		0.1	-0.005	0.0030	2.59×10^{-5}	0.0848
		0.5	-0.003	0.0030	6.33×10^{-6}	0.3940
		1	-0.003	0.0030	9.46×10^{-6}	0.2975
	Intracranial Volume	0.01	0.0001	0.0030	1.33×10^{-8}	0.9689
		0.05	0.0005	0.0030	2.09×10^{-7}	0.8768
		0.1	0.004	0.0030	1.60×10^{-5}	0.1749
		0.5	0.005	0.0030	2.55×10^{-5}	0.0872
		1	0.005	0.0030	2.71×10^{-5}	0.0778
	Infant Head Circumference	0.01	0.002	0.0030	4.94×10^{-6}	0.4514
		0.05	0.001	0.0030	1.65×10^{-6}	0.6639
		0.1	0.005	0.0030	2.70×10^{-5}	0.0782
		0.5	0.003	0.0030	7.25×10^{-6}	0.3616
		1	0.002	0.0030	4.00×10^{-6}	0.4979
Physical and physiological measures	Blood Pressure: Diastolic	0.01	0.002	0.0030	3.37×10^{-6}	0.5342
		0.05	-0.001	0.0030	4.65×10^{-7}	0.8173
		0.1	0.001	0.0030	1.22×10^{-6}	0.7082
		0.5	-0.001	0.0030	2.10×10^{-6}	0.6232
		1	-0.002	0.0030	3.37×10^{-6}	0.5342
	Blood Pressure: Systolic	0.01	-0.002	0.0030	5.00×10^{-6}	0.4488
		0.05	-0.003	0.0030	8.80×10^{-6}	0.3149
		0.1	-0.002	0.0030	3.04×10^{-6}	0.5551
		0.5	-0.003	0.0030	8.72×10^{-6}	0.3172
		1	-0.002	0.0030	5.24×10^{-6}	0.4383
	BMI	0.01	0.008	0.0030	6.75×10^{-5}	0.0054
		0.05	0.013	0.0030	0.00016	1.85×10^{-5}
		0.1	0.016	0.0030	0.000253	7.31×10^{-8}

Life-course Cognitive Traits and Proxies	Height		0.5	0.014	0.0030	0.000191	2.76×10⁻⁶
			1	0.014	0.0030	0.00019	3.05×10⁻⁶
			0.01	0.003	0.0030	7.37×10 ⁻⁶	0.3579
			0.05	0.001	0.0030	1.71×10 ⁻⁶	0.6581
			0.1	0.001	0.0030	1.92×10 ⁻⁶	0.6390
	Longevity		0.5	0.001	0.0031	1.51×10 ⁻⁶	0.6772
			1	0.001	0.0031	7.45×10 ⁻⁷	0.7700
			0.01	0.004	0.0030	1.77×10 ⁻⁵	0.1538
			0.05	0.003	0.0030	1.17×10 ⁻⁵	0.2473
			0.1	0.005	0.0030	2.25×10 ⁻⁵	0.1078
	Forced Expiratory Volume in 1s (FEV ₁)		0.5	0.005	0.0030	2.70×10 ⁻⁵	0.0783
			1	0.006	0.0030	3.39×10 ⁻⁵	0.0484
			0.01	-0.005	0.0030	2.29×10 ⁻⁵	0.1048
			0.05	-0.005	0.0030	2.55×10 ⁻⁵	0.0870
			0.1	-0.004	0.0030	2.00×10 ⁻⁵	0.1302
	Childhood Cognitive Ability		0.5	-0.005	0.0030	2.44×10 ⁻⁵	0.0945
			1	-0.005	0.0030	2.60×10 ⁻⁵	0.0840
			0.01	0.004	0.0030	1.51×10 ⁻⁵	0.1884
			0.05	0.006	0.0030	3.23×10 ⁻⁵	0.0541
			0.1	0.008	0.0030	5.61×10 ⁻⁵	0.0112
	College degree		0.5	0.014	0.0030	0.0001	4.25×10⁻⁶
			1	0.014	0.0030	0.0002	1.65×10⁻⁶
			0.01	0.0005	0.0030	2.78×10 ⁻⁷	0.8583
			0.05	-0.002	0.0030	4.55×10 ⁻⁶	0.4698
			0.1	-0.002	0.0030	4.57×10 ⁻⁶	0.4688
	Years of Education		0.5	0.001	0.0030	1.61×10 ⁻⁶	0.6669
			1	0.002	0.0030	2.63×10 ⁻⁶	0.5826
			0.01	-0.0003	0.0030	7.68×10 ⁻⁸	0.9252
			0.05	-0.004	0.0030	1.75×10 ⁻⁵	0.1563
			0.1	-0.004	0.0030	1.21×10 ⁻⁵	0.2377
			0.5	-0.002	0.0030	5.43×10 ⁻⁶	0.4299
			1	-0.002	0.0030	2.28×10 ⁻⁶	0.6089

Supplementary Table 4d

Associations between polygenic profiles of health related traits, and college controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values ($P < 0.0188$) are shown in bold. Cognitive/education phenotypes are scored such that higher scores indicate better performance.

Trait category	Trait	Educational Attainment				
		Threshold	β	SE	R ²	p
Vascular-Metabolic Diseases	Coronary Artery Disease	0.01	-0.020	0.0066	0.0001	0.0020
		0.05	-0.026	0.0066	0.0002	0.0001
		0.1	-0.033	0.0066	0.0003	8.09×10⁻⁷
		0.5	-0.047	0.0066	0.0006	8.32×10⁻¹³
		1	-0.047	0.0066	0.0006	7.92×10⁻¹³
	Stroke: Ischaemic	0.01	-0.013	0.0066	4.64×10 ⁻⁵	0.0539
		0.05	-0.020	0.0067	0.0001	0.0032
		0.1	-0.016	0.0067	0.0001	0.0171
		0.5	-0.020	0.0068	0.0001	0.0026
		1	-0.013	0.0068	4.67×10 ⁻⁵	0.0534
	Stroke: Cardioembolic	0.01	-0.0001	0.0066	6.41×10 ⁻⁹	0.9819
		0.05	-0.001	0.0066	1.43×10 ⁻⁷	0.9148
		0.1	0.001	0.0066	2.76×10 ⁻⁷	0.8817
		0.5	-0.003	0.0066	1.94×10 ⁻⁶	0.6931
		1	0.000	0.0066	4.94×10 ⁻¹²	0.9995
	Stroke: Large Vessel Disease	0.01	-0.023	0.0066	0.0002	0.0005
		0.05	-0.025	0.0067	0.0002	0.0001
		0.1	-0.031	0.0067	0.0003	5.31×10⁻⁶
		0.5	0.008	0.0066	1.70×10 ⁻⁵	0.2438
		1	0.001	0.0066	5.27×10 ⁻⁷	0.8372
	Stroke: Small Vessel Disease	0.01	-0.024	0.0066	0.0002	0.0003
		0.05	-0.030	0.0066	0.0003	5.89×10⁻⁶
		0.1	-0.034	0.0066	0.0003	2.96×10⁻⁷
		0.5	0.000	0.0066	3.41×10 ⁻⁸	0.9583
		1	0.002	0.0066	1.15×10 ⁻⁶	0.7615
	Type 2 Diabetes	0.01	-0.023	0.0066	0.0001	0.0006
		0.05	-0.021	0.0067	0.0001	0.0020
		0.1	-0.025	0.0067	0.0002	0.0002
		0.5	-0.025	0.0067	0.0002	0.0002
		1	-0.024	0.0068	0.0002	0.0003
Neuro-Psychiatric Disorders	ADHD	0.01	-0.010	0.0066	2.73×10 ⁻⁵	0.1391
		0.05	-0.016	0.0066	0.0001	0.0138
		0.1	-0.022	0.0066	0.0001	0.0007
		0.5	-0.025	0.0066	0.0002	0.0001
		1	-0.027	0.0066	0.0002	4.68×10⁻⁵
	Alzheimer's Disease	0.01	-0.013	0.0066	4.51×10 ⁻⁵	0.0572
		0.05	-0.034	0.0066	0.0003	2.53×10⁻⁷
		0.1	-0.038	0.0066	0.0004	7.00×10⁻⁹
		0.5	-0.046	0.0066	0.0006	2.52×10⁻¹²
		1	-0.046	0.0066	0.0006	2.33×10⁻¹²

Brain Measures	Autism	0.01	0.046	0.0066	0.0006	4.09×10^{-12}
		0.05	0.061	0.0066	0.0011	1.68×10^{-20}
		0.1	0.060	0.0066	0.0010	1.42×10^{-19}
		0.5	0.068	0.0066	0.0013	5.00×10^{-25}
		1	0.067	0.0066	0.0013	2.88×10^{-24}
	Bipolar Disorder	0.01	0.032	0.0066	0.0003	9.40×10^{-7}
		0.05	0.046	0.0066	0.0006	3.80×10^{-12}
		0.1	0.050	0.0066	0.0007	3.41×10^{-14}
		0.5	0.057	0.0067	0.0009	1.35×10^{-17}
		1	0.055	0.0067	0.0008	2.60×10^{-16}
	Major Depressive Disorder	0.01	0.004	0.0066	4.03×10^{-6}	0.5700
		0.05	0.003	0.0066	2.61×10^{-6}	0.6475
		0.1	0.003	0.0067	2.22×10^{-6}	0.6731
		0.5	-0.006	0.0067	1.14×10^{-5}	0.3400
		1	-0.009	0.0067	2.14×10^{-5}	0.1905
	Schizophrenia	0.01	0.022	0.0066	0.0001	0.0008
		0.05	0.025	0.0067	0.0002	0.0002
		0.1	0.024	0.0067	0.0002	0.0004
		0.5	0.022	0.0068	0.0001	0.0012
		1	0.021	0.0068	0.0001	0.0017
	Hippocampal Volume	0.01	-0.007	0.0066	1.27×10^{-5}	0.3132
		0.05	-0.001	0.0066	6.01×10^{-7}	0.8262
		0.1	0.005	0.0066	6.29×10^{-6}	0.4778
		0.5	0.007	0.0066	1.40×10^{-5}	0.2887
		1	0.005	0.0066	8.49×10^{-6}	0.4095
	Intracranial Volume	0.01	0.031	0.0066	2.81×10^{-4}	2.08×10^{-6}
		0.05	0.034	0.0067	0.0003	4.30×10^{-7}
		0.1	0.039	0.0067	0.0004	7.92×10^{-9}
		0.5	0.041	0.0068	0.0005	8.86×10^{-10}
		1	0.043	0.0068	0.0005	2.91×10^{-10}
	Infant Head Circumference	0.01	0.035	0.0066	0.0003	1.64×10^{-7}
		0.05	0.038	0.0066	0.0004	6.43×10^{-9}
		0.1	0.050	0.0066	0.0007	4.01×10^{-14}
		0.5	0.049	0.0067	0.0007	1.37×10^{-13}
		1	0.049	0.0067	0.0007	2.32×10^{-13}
Physical and physiological measures	Blood Pressure: Diastolic	0.01	0.004	0.0066	5.75×10^{-6}	0.4971
		0.05	0.020	0.0066	0.0001	0.0022
		0.1	0.022	0.0066	0.0001	0.0011
		0.5	0.020	0.0066	0.0001	0.0028
		1	0.018	0.0066	0.0001	0.0053
	Blood Pressure: Systolic	0.01	0.017	0.0066	0.0001	0.0095
		0.05	0.032	0.0066	0.0003	8.25×10^{-7}
		0.1	0.035	0.0066	0.0004	7.61×10^{-8}
		0.5	0.027	0.0066	0.0002	4.66×10^{-5}
		1	0.027	0.0066	0.0002	4.35×10^{-5}
	BMI	0.01	-0.065	0.0066	0.0012	3.15×10^{-23}
		0.05	-0.074	0.0066	0.0016	2.80×10^{-29}

Life-course Cognitive Traits and Proxies	Height		0.1	-0.081	0.0066	0.0019	7.97×10^{-35}
			0.5	-0.093	0.0066	0.0025	6.40×10^{-45}
			1	-0.093	0.0066	0.0025	1.07×10^{-44}
			0.01	0.054	0.0067	0.0008	8.35×10^{-16}
			0.05	0.062	0.0067	0.0011	3.00×10^{-20}
			0.1	0.066	0.0068	0.0012	9.82×10^{-23}
	Longevity		0.5	0.069	0.0069	0.0013	4.84×10^{-24}
			1	0.070	0.0069	0.0013	2.95×10^{-24}
			0.01	NA	NA	NA	NA
			0.05	NA	NA	NA	NA
			0.1	NA	NA	NA	NA
			0.5	NA	NA	NA	NA
	Forced Expiratory Volume in 1s (FEV ₁)		1	NA	NA	NA	NA
			0.01	NA	NA	NA	NA
			0.05	NA	NA	NA	NA
			0.1	NA	NA	NA	NA
			0.5	NA	NA	NA	NA
			1	NA	NA	NA	NA
	Childhood Cognitive Ability		0.01	0.062	0.0066	0.0011	5.29×10^{-21}
			0.05	0.095	0.0066	0.0026	1.67×10^{-46}
			0.1	0.106	0.0066	0.0032	4.17×10^{-58}
			0.5	0.120	0.0066	0.0041	9.28×10^{-74}
			1	0.122	0.0066	0.0042	3.92×10^{-75}
			0.01	0.205	0.0067	0.0118	1.47×10^{-206}
	College degree		0.05	0.251	0.0067	0.0175	1.60×10^{-303}
			0.1	0.265	0.0068	0.0194	0
			0.5	0.280	0.0068	0.0216	0
			1	0.279	0.0068	0.0214	0
	Years of Education		0.01	0.210	0.0067	0.0124	1.56×10^{-216}
			0.05	0.244	0.0067	0.0167	5.61×10^{-289}
			0.1	0.265	0.0068	0.0195	0
			0.5	0.283	0.0068	0.0220	0
			1	0.285	0.0068	0.0223	0

Supplementary Table 5

Multivariate models predicting cognitive (and educational) phenotypes, including all polygenic profile scores together with covariates (age, sex, assessment centre, genotyping batch and array, and ten genetic principal components for population structure; covariate values not shown here). All phenotypes scored such that higher scores indicate better performance. Adjusted R^2 values refer to the polygenic profile scores only (excluding variance explained by the covariates). Statistically significant p-values (after False Discovery Rate correction across 94 tests; threshold: $p < 0.025$) shown in bold.

Trait Category	Trait	Verbal-numerical Reasoning (Adj. $R^2 = 0.0226$)			Memory (Adj. $R^2 = 0.0017$)			Reaction Time (Adj. $R^2 = 0.0012$)			Educational Attainment (Adj. $R^2 = 0.0333$)		
		β	p		β	p		β	p		β	p	
Vascular-metabolic Diseases	Coronary Artery Disease	-0.012	0.021		-0.002	0.506		0.006	0.032		-0.034	<0.001	
	Stroke: Ischaemic	-0.009	0.102		-0.002	0.631		-0.006	0.034		0.002	0.750	
	Stroke: Cardioembolic	-0.006	0.204		0.004	0.205		0.005	0.092		0.001	0.884	
	Stroke: Large Vessel Disease	-0.008	0.141		-0.010	0.002		0.002	0.410		-0.022	0.002	
	Stroke: Small Vessel Disease	-0.008	0.113		-0.005	0.097		-0.003	0.338		-0.028	<0.001	
Neuro-psychiatric Disorders	Type 2 Diabetes	0.004	0.499		0.002	0.510		-0.002	0.450		-0.005	0.484	
	ADHD	-0.007	0.170		-0.003	0.253		-0.004	0.194		-0.018	0.007	
	Alzheimer's Disease	-0.018	<0.001		-0.008	0.007		-0.005	0.089		-0.034	<0.001	
	Autism	0.018	<0.001		0.004	0.224		0.004	0.147		0.060	<0.001	
	Bipolar Disorder	0.006	0.232		-0.006	0.068		-0.003	0.222		0.045	<0.001	
Brain Measures	Major Depressive Disorder	-0.010	0.061		-0.006	0.053		-0.006	0.025		-0.010	0.147	
	Schizophrenia	-0.061	<0.001		-0.029	<0.001		-0.028	<0.001		0.016	0.022	
	Hippocampal Volume	0.005	0.289		-0.004	0.126		0.004	0.121		0.009	0.168	
	Intracranial Volume	0.009	0.080		0.005	0.103		0.003	0.282		0.025	<0.001	
	Infant Head Circumference	0.015	0.004		0.001	0.653		-0.010	<0.001		0.041	<0.001	
Physical and Physiological Measures	BMI	-0.014	0.007		0.015	<0.001		0.003	0.311		-0.058	<0.001	
	Diastolic Blood Pressure	-0.007	0.273		0.004	0.278		0.001	0.635		0.001	0.940	
	Height	0.004	0.484		-0.001	0.681		0.001	0.830		0.037	<0.001	
	Longevity	0.003	0.526		0.005	0.068		0.002	0.491		-	-	
	Forced Expiratory Volume in 1s	0.009	0.076		-0.004	0.143		-0.003	0.222		-	-	
Life-course Cognitive Traits and Proxies	Systolic Blood Pressure	0.004	0.538		0.001	0.974		-0.005	0.212		0.015	0.082	
	Childhood Cognitive Ability	0.063	<0.001		0.011	<0.001		0.008	0.004		0.095	<0.001	
	College Degree	0.046	<0.001		0.004	0.285		0.005	0.193		0.140	<0.001	
	Years of Education	0.064	<0.001		-0.003	0.360		0.005	0.187		0.162	<0.001	

Appendix 2. Supplementary material to Section 4.3

Supplementary Materials for:

Cognitive ability and physical health: a Mendelian randomization study

Saskia P Hagenaars, Catharine R Gale, Ian J Deary and Sarah E Harris

Contents

Supplementary Figure 1: Educational attainment and verbal-numerical reasoning in UK

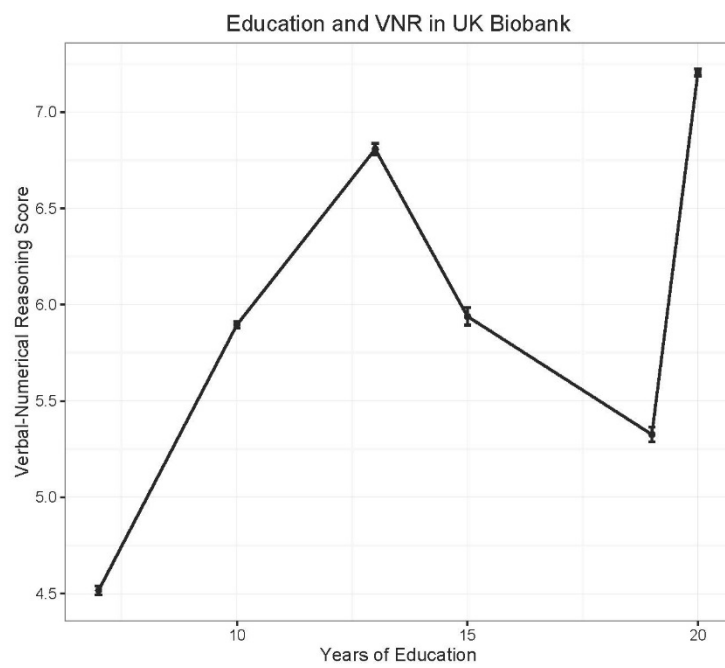
Biobank

Supplementary Table 1: Power calculations

Supplementary Table 2: Observational associations between educational attainment and health outcomes.

Supplementary Table 3a-f: Summary of the SNPs used for instrumental variants previously identified as associated with exposure at genome wide significance

Supplementary figure 1. Educational attainment categories and mean scores for verbal-numerical reasoning per group. Error bars represent standard errors.



Supplementary Table 1. Power for bidirectional Mendelian randomization analysis (two-sided $\alpha = 0.05$). Power calculations are based on the method developed by Brion, et al.¹.

Exposure/instrumental variable	Outcome	R-squared (of variance in exposure)	Actual N (outcome)	Proportion of cases (outcome)	Observational Effect size	N required for 80% power	Power at actual N
Educational attainment	BMI	0.015	111712	NA	-0.37	3299	1
Educational attainment	Height	0.015	111959	NA	0.31	4922	1
Educational attainment	Systolic blood pressure	0.015	106759	NA	-0.2	12559	1
Educational attainment	Coronary artery disease	0.015	110,072	0.048	OR 0.4	42,832	1
Educational attainment	Type 2 diabetes	0.015	111,779	0.034	OR 0.6	86,084	0.89
BMI	Verbal-numerical reasoning	0.027	36,035	NA	-0.05	115990	0.35
Height	Verbal-numerical reasoning	0.15	36,035	NA	0.18	1563	1
Systolic blood pressure	Verbal-numerical reasoning	0.009	36,035	NA	-0.05	347968	0.15
Coronary artery disease	Verbal-numerical reasoning	0.1	36,035	NA	-0.27	999	1
Type 2 diabetes	Verbal-numerical reasoning	0.057	36,035	NA	-0.06	36207	0.8

Supplementary Table 2. Observational associations between educational attainment and health outcomes.

	Educational attainment – health outcomes (7 vs 10 years)			Educational attainment – health outcomes (7 vs 13 years)		
	Beta	95% CI	p	Beta	95% CI	p
BMI	-0.1287	-0.146 – (-0.111)	7.25 * 10⁻⁴⁴	-0.2350	-0.257 – (-0.213)	8.15 * 10⁻⁹³
Height	0.1667	0.155 – 0.178	2.25 * 10⁻¹⁵¹	0.2590	0.243 – 0.275	1.94 * 10⁻²³⁵
Systolic blood pressure	-0.0775	-0.095 – (-0.060)	6.89 * 10⁻¹⁸	-0.1273	-0.149 – (-0.106)	1.71 * 10⁻³⁰
Type 2 diabetes	OR: 0.815	0.742 – 0.895	1.74 * 10⁻⁰⁵	OR: 0.800	0.706 – 0.905	4.27 * 10⁻⁰⁴
Coronary artery disease	OR: 0.631	0.583 – 0.683	2.79 * 10⁻³⁰	OR: 0.555	0.496 – 0.620	2.98 * 10⁻²⁵

Supplementary Table 3a-f. Summary of the SNPs used for instrumental variants previously identified as associated with exposure at genome wide significance.

(See Supplementary Table at the following URL:

<http://biorxiv.org/content/biorxiv/suppl/2017/03/09/084798.DC2/084798-2.pdf>)

References

1 Brion, M.-J. A., Shakhbazov, K. & Visscher, P. M. Calculating statistical power in Mendelian randomization studies. *International Journal of Epidemiology* 42, 1497-1501, doi:10.1093/ije/dyt179 (2013)

Appendix 3. Supplementary material to Section 5.2

Supplementary material

Hagenaars et al. Genetic contributions to trail making test performance in UK Biobank.

Supplementary Methods

Cognitive measures in Generation Scotland and LBC1936

Adjusting heritability for reliability of measures

Supplementary Tables and Figures

Supplementary Figure 1: Trail making test in UK Biobank

Supplementary Figure 2: Age-sex distributions for trail making test in UK Biobank.

Supplementary Table 1: Gene-based results conducted on trail making test.

Supplementary Table 2: Adjusted heritability estimates

Supplementary Table 3: Complete polygenic profile score associations with trail making using all five thresholds in UK Biobank, GS and LBC1936.

Supplementary Figure 3: Manhattan plots for meta-analysis of trail making in UK Biobank and CHARGE.

Supplementary Figure 4: Age distribution for trail making measures and verbal-numerical reasoning in UK Biobank.

Acknowledgements

Cognitive measures

Generation Scotland (GS)

All participants in GS were invited to complete a short battery of well-validated cognitive tests, personal and family medical history details were taken during a clinical interview. The four cognitive tests were the Mill Hill Vocabulary test (combined Junior and Senior synonyms)¹, Logical Memory in the Wechsler Memory Scale III (WMS-III, the sum of immediate and delayed recall for one paragraph)², the phonemic Verbal Fluency test (using letters C, F, and L)³ and Digit Symbol-Coding from the Wechsler Adult Intelligence Scale III (WAIS-III)⁴.

Lothian Birth Cohort 1936 (LBC1936)

The MHT test scores were converted to a scale with a mean of 100 and SD = 15 for each sample, as described elsewhere⁵. The following cognitive functions were derived from the cognitive test battery: trail making test Part B, fluid cognitive function, verbal cognitive function, memory, processing speed. Fluid cognitive function, the first unrotated component of a principal component analysis (PCA), was derived using the WMS-III Digit Span Backwards and WAIS-III Matrix Reasoning, Letter-Number Sequencing, Block Design, Symbol Search and Digit Symbol. Verbal cognitive function was assessed by the National Adult Reading Test (NART)⁶. Memory was derived via PCA using WMS-III Logical Memory I total recall score, Logical Memory II Delayed total recall score, Spatial Span Forward, Spatial Span Backward, Verbal Paired Associates I, Verbal Paired Associates II recall total score, and WAIS-III Letter-Number Sequencing and Digit Span Backwards. Processing speed was derived via PCA using Choice Reaction Time Mean, Simple Reaction Time mean, Digit Symbol, Inspection Time and Symbol Search in LBC1936^{7,8}. The change in cognitive function between childhood and old age was calculated using a linear regression model that summarizes the relation between the MHT test scores at age 11 and age 70. In this model, the residual values reflect the observed deviation of the MHT test scores at age 70 based on the MHT test scores predicted at age 11, representing an estimate for change in cognitive function.

Adjusting heritability estimates for reliability

It is likely that the difference score exhibits lower reliability than parts A or B alone⁹. We therefore adjusted all three heritability estimates for the purposes of comparing the relative impact of phenotypic reliability invariance (across Trails A, Trails B and Trails B-A). While reliability data are currently unavailable for the TMT in UK Biobank, we used data from a large test-retest reliability study (the connections test from Salthouse et al.¹⁰, n = 207), from which we used the reported reliability indices (which they obtained by the Spearman-Brown formula) in analogous test components to Trails A ('numbers', r = 0.88) and Trails B ('letters and numbers', r = 0.81) to derive an estimate of the reliability of the contrast score (i.e. B-A) according to Crocker & Aligned⁹, Webb et al.¹¹,

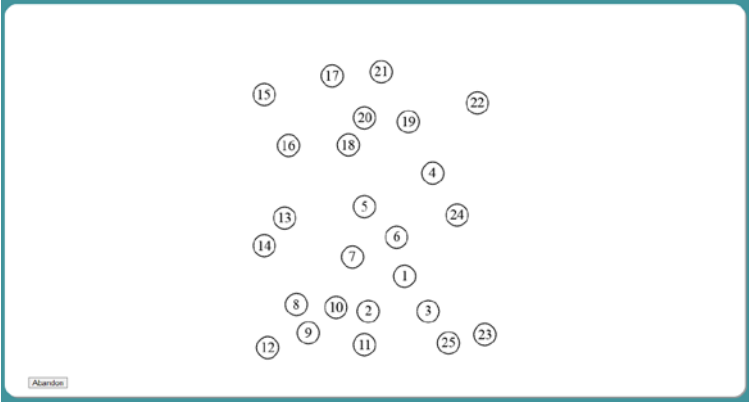
$$r_{DD} = \frac{0.5(r_{XX} + r_{YY}) - r_{XY}}{1 - r_{XY}},$$

where r_{XX} and r_{YY} are the reliabilities of the Trails components, and r_{XY} is their correlation. This gives a reliability estimate of the Trails B-A of 0.58. These reliability estimates were then used to illustrate the impact that a lower reliability of the contrast score might have on GCTA estimates, such that

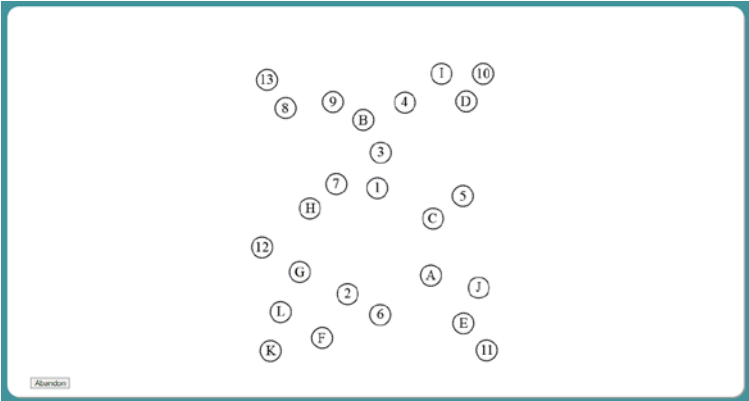
$$h2' = \frac{h2}{\sqrt{r_{XX}r_{YY}}}$$

where the adjusted heritability estimate ($h2'$) of a phenotype (X) is derived by dividing the heritability ($h2$) by the square root of the product of phenotype and genotype reliability estimates (r_{XX} and r_{YY} , respectively; after Spearman^{12,13}). The measure of relatedness (based on the gene array markers) is assumed to be 1 as this is constant across the three TMT measures. Standard errors are derived using the same formula.

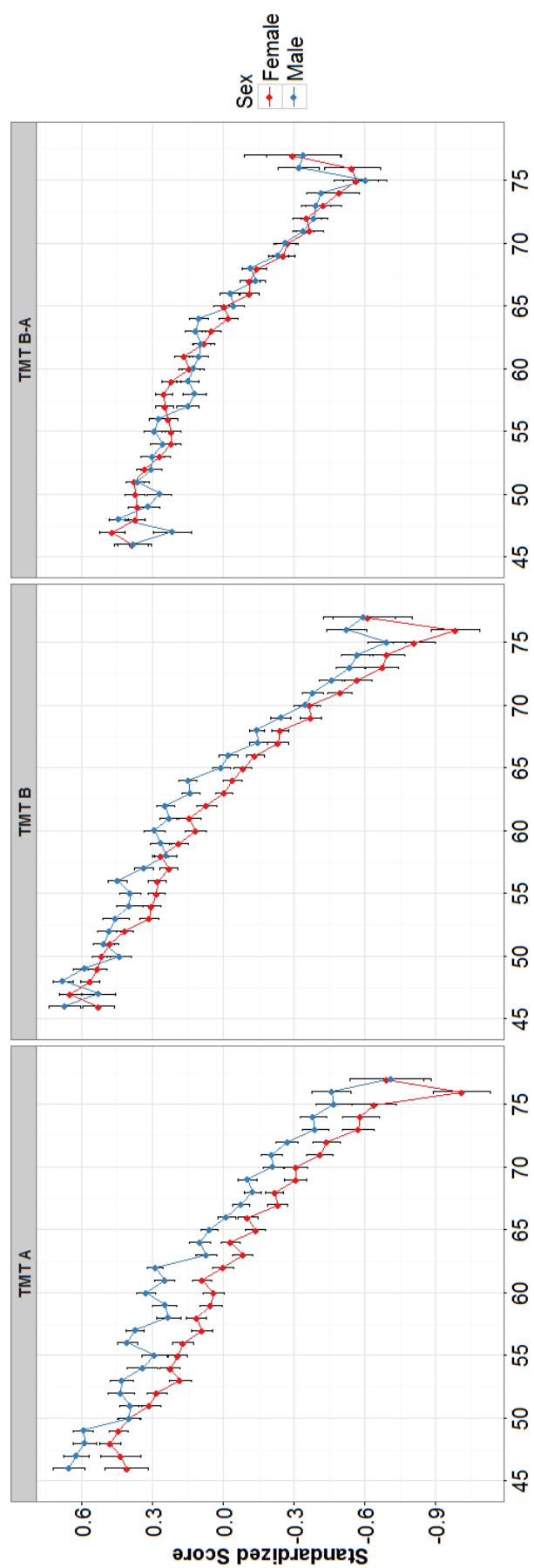
Supplementary Figure 1A. Trail making test Part A as presented in the UK Biobank web-based assessment⁹.



Supplementary Figure 1B. Trail making test Part B as presented in the UK Biobank web-based assessment¹⁰.



Supplementary Figure 2. Age-sex distributions with standard error bars for Trail Making Part A (TMT A), Trail Making Part B (TMT B), and Trail Making Part B – Part A (TMT B-A) in UK Biobank.



Supplementary Table 1a-c. Gene based analysis conducted on trail making measures using common variants (MAF >0.01). MAGMA; bold indicates genome wide significance alpha = (0.05/ 18062) CHR, chromosome; NSNPS, indicates the number of SNPs found within the start and stop sites.

(See Supplementary Tables at following URL:
<http://biorxiv.org/content/early/2017/01/25/103119.figures-only>)

Supplementary Table 2. GCTA heritability estimates for the trail making tests indices in UK Biobank, before and after adjusting for differences in phenotype reliability.

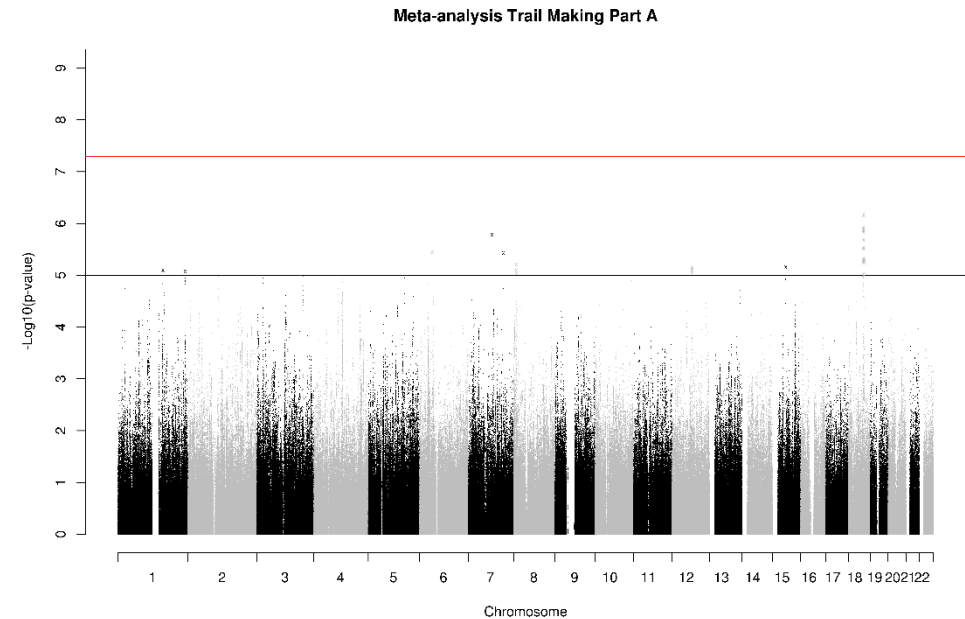
	TMT A	TMT B	TMT B-A
h2	0.079 (0.025)	0.224 (0.026)	0.176 (0.025)
h2'	0.084 (0.027)	0.249 (0.029)	0.231 (0.033)

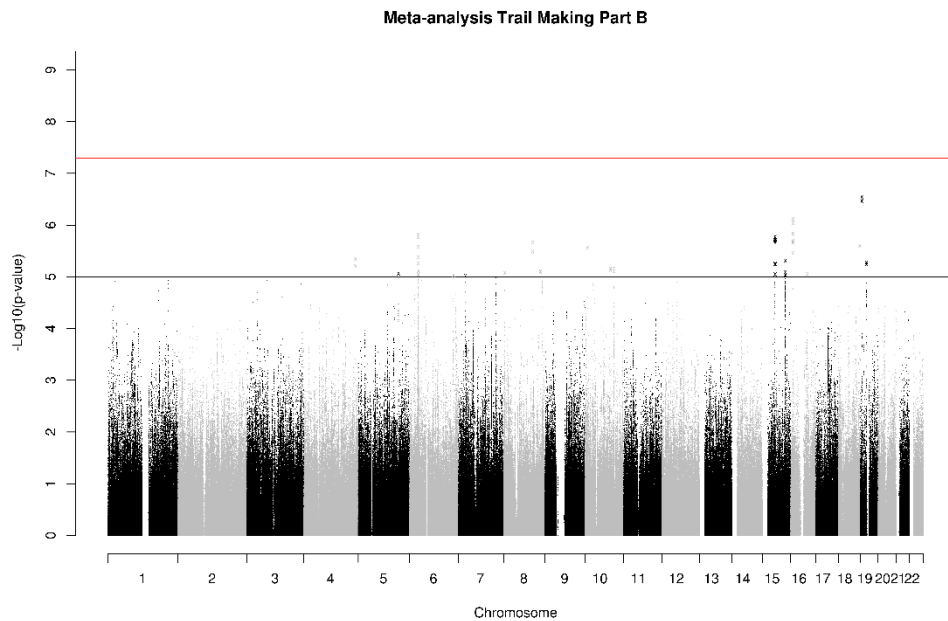
Note. Heritability with standard errors are reported before (h2) and after (h2') correction for estimated differences in test component reliabilities (see Supplementary Methods). TMT A, trail making part A; TMT B, trail making part B; TMT B-A, trail making part B minus trail making part A.

Supplementary Table 3a-c. Complete polygenic profile score associations with trail making using all five thresholds in UK Biobank, Generation Scotland and the Lothian Birth Cohort 1936.

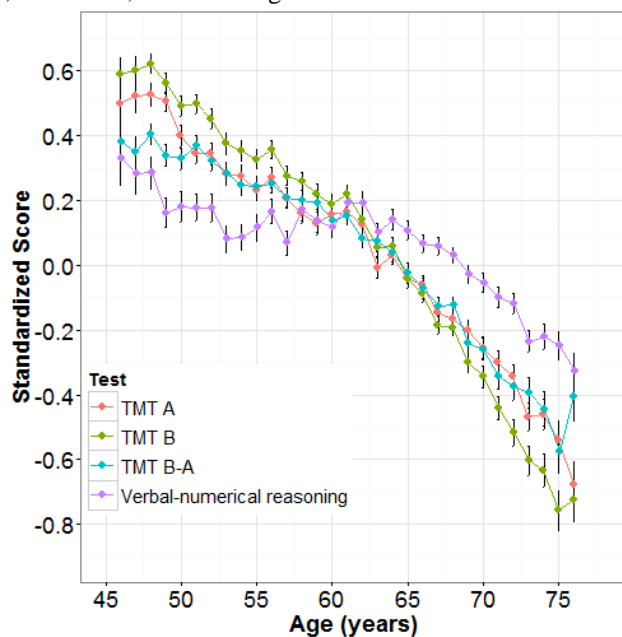
(See Supplementary Tables at following URL:
<http://biorxiv.org/content/early/2017/01/25/103119.figures-only>)

Supplementary Figure 3. Manhattan plot of P-values of the SNP-based association analysis of meta-analysis between UK Biobank and CHARGE for Trail Making Part A and Trail Making Part B. The red line indicates the threshold for genome-wide significance ($P < 5 \times 10^{-8}$); the grey line indicates the threshold for suggestive significance ($P < 1 \times 10^{-5}$).





Supplementary Figure 4. Age distribution with standard error bars for trail making measures and verbal-numerical reasoning in UK Biobank. TMT A, Trail Making Part A; TMT B, Trail Making Part B; TMT B-A, Trail Making Part B – Part A.



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1. Davies G. et al. Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53949). *Molecular Psychiatry* 20:183-192, 2015

2. DeBette S et al. Genome-wide studies of verbal declarative memory in nondemented older people: the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium. *Biological Psychiatry* 77:749-763, 2015
3. Ibrahim-Verbaas CA et al. GWAS for executive function and processing speed suggests involvement of the CADM2 gene. *Molecular Psychiatry* 21:189-197, 2016

Hieab Adams^{1,2}, David Ames^{3,4}, Helene Amieva⁵, Najaf Amin^{2,6}, Philippe Amouyel⁷, Yang An⁸, Nicola J Armstrong^{9,10,11,12}, Amelia A Assareh⁹, John R Attia¹³, Rhoda Au^{14,15}, Stefania Bandinelli¹⁶, Albert Becker¹⁷, James T Becker^{18,19,20}, Alexa Beiser^{14,15,21}, David A Bennett²², Claudine Berr^{23,24}, Lars Bertram^{25,26}, Joshua C Bis²⁷, Eric Boerwinkle^{28,29,30}, Ruth Boxall³¹, Jan Bressler²⁸, Monique MB Breteler^{1,2,32,33,34}, Henry Brodaty^{9,35}, Brendan M. Buckley³⁶, Harry Campbell³⁷, Daniel I Chasman³⁸, Ganesh Chauhan⁵, Lori B Chibnik³⁹, Seung Hoan Choi²¹, Vincent Chouraki^{7,14,40}, Sven Cichon^{41,42,43}, Laura H Coker⁴⁴, Janie Corley⁴⁵, Jean-Francois Dartigues^{5,46}, Gail Davies^{45,47}, Ian J Deary^{45,47}, Stephanie DeBette^{5,14,46}, Anton JM de Craen^{2,48}, Philip L De Jager^{39,49,50}, Dominique JF de Quervain⁵¹, Anita L DeStefano^{14,15,21}, Jingzhong Ding⁵², Carole Dufouil^{5,53}, Cornelia M van Duijn^{2,6}, Gudny Eiriksdottir⁵⁴, Johan G Eriksson^{55,56,57,58,59}, Thomas Espeseth^{60,61}, Jessica D Faul⁶², Chloe Fawns-Ritchie⁴⁷, Rudolf SN Fehrmann⁶³, Luigi Ferrucci⁶⁴, Annette L Fitzpatrick^{65,66}, Ian Ford⁶⁷, Myriam Fornage^{28,29}, Lude Franke⁶³, Melissa Garcia⁶⁸, Generation Scotland⁶⁹, Sudheer Giddaluru^{70,71}, Rebecca F Gottesman⁷², Alan J Gow^{45,47}, Hans J Grabe^{73,74}, Michael E Griswold⁷⁵, Francine Grodstein^{34,76}, Vilmunder Gudnason^{54,77}, Sarah E Harris^{47,78}, Tamara B Harris^{68,79}, Nicholas D. Hastie⁸⁰, Caroline Hayward⁸⁰, Gerardo Heiss⁸¹, Stefan Herms^{41,42}, W David Hill⁴⁵, Lynne J Hocking⁸², Edith Hofer^{83,84}, Per Hoffmann^{41,42,43}, Wolfgang Hoffman⁷⁴, Albert Hofman^{1,2}, Elizabeth G Holliday¹³, Yi-Chen Hsieh^{85,86}, Jennifer Huffman⁸⁰, Carla A Ibrahim-Verbaas^{6,87}, M Arfan Ikram^{1,2,87,88}, Maria K Jonsdottir^{54,89}, J Wouter Jukema^{90,91,92}, Nazanin Karbalai⁹³, Sharon LR Kardinaal⁹⁴, Juha Karjalainen⁶³, Richard E Kennedy⁹⁵, Mirna Kirin³⁷, Nicole A Kochan^{9,96}, David S Knopman⁹⁷, John B Kwok^{98,99}, Jari Lahti^{55,100}, Jean-Charles Lambert^{7,40}, Lenore J Launer^{68,79}, Sven J van der Lee⁶, Teresa Lee^{9,96}, Stephanie Le Hellard^{70,71}, Guo Li²⁷, Shu-Chen Li^{101,102}, David C Liewald^{45,47}, Ulman Lindenberger¹⁰¹, Tian Liu^{25,101}, Xuan Liu²¹, Yongmei Liu¹⁰³, David J Llewellyn¹⁰⁴, Kurt Lohman¹⁰³, Marisa Loitfelder⁸³, WT Longstreth Jr^{65,105}, Oscar L Lopez^{18,19,106}, Michelle Luciano^{45,47}, Astri J Lundervold^{107,108,109}, Anders Lundqvist¹¹⁰, Ricardo E Marioni^{31,47,111}, Karen A Mather⁹, Stela McLachlan³⁷, William M Meeks¹¹², Saira S Mirza^{1,2}, Thomas H Mosley Jr¹¹², Bertram Muller-Miyhsok^{93,113,114}, Michael Nalls¹¹⁵, Lars-Goran Nilsson¹¹⁶, Markus M Nöthen^{32,42}, Lars Nyberg^{110,117,118}, Christopher Oldmeadow¹³, Ben A Oostra^{6,119}, Aarno Palotie^{120,121,122}, Andreas Papassotiropoulos^{123,124}, Goran Papenberg^{101,125}, Alison Pattie^{45,47}, Alan Penman⁷⁵, Rodney T Perry¹²⁶, Katja Petrovic⁸³, Luke C Pilling¹²⁷, Ozren Polasek¹²⁸, David J Porteous^{47,69,78}, Iris Postmus^{2,48}, Jacqueline F Price³⁷, Lutz Priebe¹²⁹, Bruce M Psaty^{27,65,130,131}, Katri Räikkönen¹⁰⁰, Paul Redmond⁴⁵, Ivar Reinvang⁶¹, Simone Reppermund⁹, Susan M Resnick⁸, Paul Ridker³⁸, Lynda M Rose³⁸, Jerome I Rotter^{132,133,134}, Igor Rudan³⁷, Perminder S Sachdev^{9,96}, Michele M Sale¹³⁵, Carsten O Schmidt¹³⁶, Helena Schmidt^{83,137}, Reinhold Schmidt⁸³, Peter R Schofield^{138,139}, Peter W Schofield¹⁴⁰, Maaïke Schuur^{6,87}, Rodney J Scott¹³, Sudha Seshadri^{14,15}, Joshua M Shulman^{141,142}, P Eline Slagboom¹⁴³, Albert V Smith^{54,77}, Blair H Smith¹⁴⁴, Jennifer A Smith⁹⁴, Velandai Srikanth^{145,146}, John M Starr^{47,147}, Vidar M Steen^{70,71}, Oliver Stegle¹⁴⁸, Marlene Stewart³⁷, David J Stott¹⁴⁹, Qi Sun⁷⁶, John C van Swieten⁸⁷, Toshika Tanaka⁶⁴, Kent D Taylor^{133,150}, Alexander Teumer¹⁵¹, Anbupalam Thalamuthu⁹, Russell Thomson¹⁴⁵, Julian Trollor^{9,152}, Stella Trompet^{48,90}, Stephen T Turner¹⁵³, Christophe Tzourio^{5,154}, Andre G Uitterlinden^{1,2,155}, Veronique Vitart⁸⁰, Christian Vogler¹²³, Virginia G Wadley¹⁵⁶, Jing Wang^{15,21}, Galit Weinstein^{14,15}, David R Weir⁶², Rudi GJ Westendorp¹⁵⁷, Elisabeth Widen¹²¹, James F Wilson³⁷, Beverly G Windham¹¹², Christiane Wolf⁹³, Philip A Wolf^{14,15}, Alan F Wright⁸⁰, Margaret J Wright¹⁵⁸, Kristine Yaffe¹⁵⁹, Qiong Yang^{15,21}, Robin Yeo⁵, Lei Yu²², Lina Zgaga^{160,161}, Wei Zhao⁹⁴

Author affiliations:

¹Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands
²Netherlands Consortium for Healthy Ageing, Leiden, The Netherlands ³National Ageing Research Institute, Royal Melbourne Hospital, Melbourne, VIC, Australia ⁴Academic Unit for Psychiatry of Old Age, St George's Hospital, University of Melbourne, Kew, Australia ⁵Inserm U897, Epidemiology and Biostatistics, University of Bordeaux, Bordeaux, France ⁶Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands ⁷Inserm-UMR744, Institut Pasteur de Lille, Unité d'Epidémiologie et de Santé Publique, Lille, France ⁸Laboratory of Behavioral Neuroscience, National Institute on Aging, NIH, Baltimore, MD, USA ⁹Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, NSW, Australia ¹⁰School

of Mathematics and Statistics, University of Sydney, Sydney, NSW, Australia ¹¹Cancer Research Program, Garvan Institute of Medical Research, Sydney, NSW, Australia ¹²School of Mathematics & Statistics and Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia ¹³Hunter Medical Research Institute and Faculty of Health, University of Newcastle, Newcastle, NSW, Australia ¹⁴Department of Neurology, Boston University School of Medicine, Boston, MA, USA ¹⁵Framingham Heart Study, Framingham, MA, USA ¹⁶Geriatric Unit, Azienda Sanitaria Firenze (ASF), Florence, Italy ¹⁷Institute of Neuropathology, Universitätsklinikum Bonn, Bonn, Germany ¹⁸Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA ¹⁹Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA ²⁰Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA ²¹Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA ²²Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA ²³Inserm, U106, Montpellier, France ²⁴Université Montpellier I, Montpellier, France ²⁵Max Planck Institute for Molecular Genetics, Berlin, Germany ²⁶Faculty of Medicine, School of Public Health, Imperial College, London, UK ²⁷Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA ²⁸Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA ²⁹Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, University of Texas Health Science Center at Houston, Houston, TX, USA ³⁰Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA ³¹Medical Genetics Section, University of Edinburgh Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK ³²German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany ³³Population Health Sciences, University of Bonn, Bonn, Germany ³⁴Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA ³⁵Dementia Collaborative Research Centre, University of New South Wales, Sydney, NSW, Australia ³⁶Department of Pharmacology and Therapeutics, University College Cork, Cork, Ireland ³⁷Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK ³⁸Department of Medicine, Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA ³⁹Program in Translational Neuropsychiatric Genomics, Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA ⁴⁰Inserm, U1167, Institut Pasteur de Lille, Université Lille-Nord de France, Lille, France ⁴¹Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland ⁴²Department of Genomics, Life and Brain Research Center, Institute of Human Genetics, University of Bonn, Bonn, Germany ⁴³Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, Germany ⁴⁴Division of Public Health Sciences and Neurology, Wake Forest School of Medicine, Winston-Salem, NC, USA ⁴⁵Department of Psychology, University of Edinburgh, Edinburgh, UK ⁴⁶Department of Neurology, Bordeaux University Hospital, Bordeaux, France ⁴⁷Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK ⁴⁸Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands ⁴⁹Harvard Medical School, Boston, MA, USA ⁵⁰Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA ⁵¹Psychiatric University Clinics and Department of Psychology, Division of Cognitive Neuroscience, University of Basel, Basel Switzerland ⁵²Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA ⁵³Inserm U708, Neuroepidemiology, Paris, France ⁵⁴Icelandic Heart Association, Kopavogur, Iceland ⁵⁵Folkhälsan Research Centre, Helsinki, Finland ⁵⁶National Institute for Health and Welfare, Helsinki, Finland ⁵⁷Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland ⁵⁸Unit of General Practice, Helsinki University Central Hospital, Helsinki, Finland ⁵⁹Vasa Central Hospital, Vasa, Finland ⁶⁰K.G. Jebsen Centre for Psychosis Research, Norwegian Centre For Mental Disorders Research (NORMENT), Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway ⁶¹Department of Psychology, University of Oslo, Oslo, Norway ⁶²Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, USA ⁶³Department of Genetics, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands ⁶⁴Translational Gerontology Branch, National Institute on Aging, Baltimore, MD, USA ⁶⁵Department of Epidemiology, University of Washington, Seattle, WA, USA ⁶⁶Department of Global Health, University of Washington, Seattle, WA, USA ⁶⁷Robertson Center for Biostatistics, University of Glasgow, Glasgow, UK ⁶⁸Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, MD, USA ⁶⁹Generation Scotland, University of Edinburgh Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK ⁷⁰K.G. Jebsen Centre for Psychosis Research and the Norwegian Centre for Mental Disorders Research (NORMENT),

Department of Clinical Science, University of Bergen, Bergen, Norway ⁷¹Dr Einar Martens Research Group for Biological Psychiatry, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway ⁷²Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA ⁷³Department of Psychiatry and Psychotherapy, University Medicine Greifswald, HELIOS-Hospital Stralsund, Stralsund, Germany ⁷⁴German Center for Neurodegenerative Diseases, Site Rostock/Greifswald, Rostock, Germany ⁷⁵Center of Biostatistics and Bioinformatics, University of Mississippi Medical Center, Jackson, MS, USA ⁷⁶Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA ⁷⁷Faculty of Medicine, University of Iceland, Reykjavik, Iceland ⁷⁸Medical Genetics Section, University of Edinburgh Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK ⁷⁹Intramural Research Program National Institutes on Aging, National Institutes of Health, Bethesda, MD, USA ⁸⁰MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK ⁸¹Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA ⁸²Division of Applied Medicine, University of Aberdeen, Aberdeen, UK ⁸³Department of Neurology, Medical University of Graz, Graz, Austria ⁸⁴Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria ⁸⁵School of Public Health, Taipei Medical University, Taipei, Taiwan ⁸⁶Neural Regenerative Medicine, College of Medical Sciences and Technology, Taipei Medical University, Taipei, Taiwan ⁸⁷Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands ⁸⁸Department of Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands ⁸⁹Landspítali Hospital, Reykjavik, Iceland ⁹⁰Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands ⁹¹Durrer Center for Cardiogenetic Research, Amsterdam, The Netherlands ⁹²Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands ⁹³RG Statistical Genetics, Max Planck Institute of Psychiatry, Munich, Germany ⁹⁴Department of Epidemiology, University of Michigan, Ann Arbor, MI, USA ⁹⁵Division of Gerontology, Geriatrics and Palliative Care, University of Alabama at Birmingham, Birmingham, AL, USA ⁹⁶Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, NSW, Australia ⁹⁷Department of Neurology, Mayo Clinic, Rochester, MN, USA ⁹⁸Neuroscience Research Australia, Randwick, NSW, Australia ⁹⁹School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia ¹⁰⁰Institute of Behavioural Sciences, University of Helsinki, Helsinki, Finland ¹⁰¹Max Planck Institute for Human Development, Berlin, Germany ¹⁰²Technische Universität Dresden, Dresden, Germany ¹⁰³Department of Epidemiology, Wake Forest School of Medicine, Winston-Salem, NC, USA ¹⁰⁴Institute of Biomedical and Clinical Sciences, University of Exeter Medical School, Exeter, UK ¹⁰⁵Department of Neurology, University of Washington, Seattle, WA, USA ¹⁰⁶Alzheimer's Disease Research Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA ¹⁰⁷Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway ¹⁰⁸Kavli Research Centre for Aging and Dementia, Haraldsplass Deaconess Hospital, Bergen, Norway ¹⁰⁹K.G. Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway ¹¹⁰Umeå Center for Functional Brain Imaging (UFBI), Umeå University, Umeå, Sweden ¹¹¹Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia ¹¹²Department of Medicine, Division of Geriatrics, University of Mississippi Medical Center, Jackson, MS, USA ¹¹³Munich Cluster for Systems Neurology (SyNergy) Munich Germany ¹¹⁴Institute of Translational Medicine, University of Liverpool, Liverpool, UK ¹¹⁵Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA ¹¹⁶ARC, Karolinska Institutet, Stockholm and UFBI, Umeå University, Umeå, Sweden ¹¹⁷Department of Radiation Sciences, Umeå University, Umeå, Sweden ¹¹⁸Department of Integrative Medical Biology, Umeå University, Umeå, Sweden ¹¹⁹Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands ¹²⁰Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK ¹²¹Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland ¹²²Department of Medical Genetics, University of Helsinki and University Central Hospital, Helsinki, Finland ¹²³Psychiatric University Clinics and Department of Psychology, Division of Molecular Neuroscience, University of Basel, Basel, Switzerland ¹²⁴Department Biozentrum, Life Sciences Training Facility, Basel, Switzerland ¹²⁵Karolinska Institutet, Aging Research Center, Stockholm University, Stockholm, Sweden ¹²⁶Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA ¹²⁷Epidemiology and Public Health Group, University of Exeter Medical School, Exeter, UK ¹²⁸Faculty of Medicine, Department of Public Health, University of Split, Split, Croatia ¹²⁹Institute of Human Genetics, Universitätsklinikum Bonn, Bonn, Germany ¹³⁰Department of Health Services, University of Washington, Seattle, WA, USA ¹³¹Group Health Research Unit, Group Health Cooperative, Seattle,

WA, USA ¹³²Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA ¹³³Institute for Translational Genomics and Population Sciences, Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA ¹³⁴Division of Genetic Outcomes, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA ¹³⁵Center for Public Health Genomics, Department of Medicine, Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA, USA ¹³⁶Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany ¹³⁷Centre for Molecular Medicine, Institute of Molecular Biology and Biochemistry, Medical University of Graz, Graz, Austria ¹³⁸Neuroscience Research Australia, Sydney, NSW, Australia ¹³⁹Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia ¹⁴⁰School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia ¹⁴¹Department of Neurology, Baylor College of Medicine, Houston, TX, USA ¹⁴²Department of Molecular and Human Genetics, The Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, TX, USA ¹⁴³Department of Molecular Epidemiology, Leiden University Medical Center, Leiden, The Netherlands ¹⁴⁴Medical Research Institute, University of Dundee, Dundee, UK ¹⁴⁵Menzies Research Institute, University of Tasmania, Hobart, Tasmania ¹⁴⁶Stroke and Ageing Research Centre, Department of Medicine, Southern Clinical School, Monash University, Melbourne, VIC, Australia ¹⁴⁷Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK ¹⁴⁸Max Planck Institute for Developmental Biology, Max Planck Institute for Intelligent Systems, Tübingen, Germany ¹⁴⁹Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK ¹⁵⁰Department of Pediatrics, Harbor-UCLA Medical Center, Los Angeles, CA, USA ¹⁵¹Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany ¹⁵²Department of Developmental Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, NSW, Australia ¹⁵³Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA ¹⁵⁴Department of Medical Information, University Hospital of Bordeaux, Bordeaux, France ¹⁵⁵Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands ¹⁵⁶Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA ¹⁵⁷Leiden Academy of Vitality and Ageing, Leiden, The Netherlands ¹⁵⁸Neuroimaging Genetics Group, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia ¹⁵⁹Departments of Psychiatry, Neurology and Epidemiology, University of California, San Francisco and San Francisco VA Medical Center, San Francisco, CA, USA ¹⁶⁰Department of Public Health and Primary Care, Trinity College Dublin, Dublin, Ireland ¹⁶¹Andrija Stampar School of Public Health, Medical School, University of Zagreb, Zagreb, Croatia

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Appendix 4. Supplementary material to Section 6.2

Gale and Hagenaars et al. Pleiotropy between neuroticism and physical and mental health: findings from 108 038 men and women in UK Biobank.

Supplementary materials

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Genotyping and Quality Control

Genotyping was performed on 33 batches of ~4700 samples by Affymetrix, who also performed initial quality control of the genotyping data. Further details are available of the sample processing specific to the UK Biobank project (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583>) and the Axiom array (http://media.affymetrix.com/support/downloads/manuals/axiom_2_assay_auto_workflow_user_guide.pdf). Prior to the release of the UK Biobank genetic data a stringent QC protocol was applied, and performed at the Wellcome Trust Centre for Human Genetics (WTCHG); details of this process can be found at the following URL (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580>). Prior to the analyses described in the main report, further quality control measures were applied by the present authors. Individuals were removed based on missingness, relatedness (KING estimated kinship co-efficient > 0.0442), gender mismatch, non-British ancestry (principal component analysis identified probable Caucasians within those individuals that were self-identified as British), and QC failure in the UK BiLEVE study. A sample of 112 151 individuals remained for further analyses. A minor allele frequency of maf < 1% filter was applied and only autosomal variants were used in this study (N = 705 516).

Genome-wide association analyses (GWAS) in the UK Biobank sample

An imputed dataset, including >70 million variants, was made available in which the UK Biobank interim release was imputed to a reference set which combined the UK10K haplotype and 1000 Genomes Phase 3 reference panels. Further details can be found at the following URL: <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020>. A genome-wide association analysis of neuroticism was performed on the imputed dataset using SNPTest v2.5.1 (Marchini J, Howie B, Myers S, et al. A new multipoint method for genome-wide association studies via imputation of genotypes. Nat Genet 2007; 39: 906-913; SNPTTEST v.2.5.1 can be found at the following URL: https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html#introduction). An additive model was specified using the "frequentist 1" option. To account for genotype uncertainty we analysed the expected genotyped counts (dosages). Adjustments for age, sex, genotyping batch, genotyping array, assessment centre and 10 principal components were included. Prior to use in LD regression analyses the association results were filtered based on minor allele frequency (<0.1%) and imputation quality (<0.1).

LD regression genetic correlation procedure

Where available in the summary statistics provided, a MAF threshold of > 0.01 was applied. To control for imputation quality, only those SNPs found in the HapMap3 with 1000 Genomes EUR with a MAF > 0.05 were included (integrated_phase1_v3.20101123). Next, indels and structural variants were removed along with strand-ambiguous SNPs. Finally, genome-wide significant SNPs were removed, as were SNPs with very large effect sizes ($\chi^2 > 80$), as the presence of outliers can increase the standard error in a regression model. LD scores and weights for use with the GWAS of European ancestry were downloaded from the Broad institute (http://www.broadinstitute.org/~bulik/eur_ldscores/). Data sets demonstrating a heritability Z-score (h^2_z) > 4 and a mean χ^2 statistic of > 1.02 were included. All traits, except negative affect and borderline personality, exceeded these thresholds. An unconstrained intercept was used in the regression model as it was not possible to quantify the degree of sample overlap between the genome-wide association analyses used here.

Polygenic profiling procedure

The genetic data files (.map and .ped files) supplied from Biota (the UK Biobank online repository) were unsuitable for use in the polygenic profile analyses as the .ped allele coding used a 1, 2 numeric allele encode rather than the standard ACGT encode format. In order to enable the analysis, the .ped files were recoded to the standard encode format. To achieve this, a bespoke programme was developed to create new files using a lookup-substitution method. A fast-in-memory lookup string hash table was created to hold the SNP-ID, along with the allele identifiers for the SNP. A simple loop then performed serialised lookups based on string position, to create an associated string with the correct ACGT encode. This was then appended to the six mandatory data fields extracted from initial string. In order to maximise performance and enable timely completion of the lookup-substitution, these loops were run in parallel threads in a standard multiprocessor environment.

Sources of genetic results from genome-wide association consortia

CARDIoGRAM

Coronary artery disease data have been contributed by CARDIoGRAMplusC4D investigators.

CHARGE-Aging and Longevity

Longevity data have been provided by the CHARGE-Aging and Longevity consortium. Longevity was defined as reaching age 90 years or older. Genotyped participants who died between the ages of 55 and 80 years were used as the control group. There were 6036 participants who achieved longevity and 3757 participants in the control group across participating studies in the discovery meta-analysis.

Broer L, Buchman AS, Deelen J, Evans DS, Faul JD, Lunetta KL, Sebastiani P, Smith JA, Smith AV, Tanaka T, Yu L, Arnold AM, Aspelund T, Benjamin EJ, De Jager PL, Eiriksdottir G, Evans DA, Garcia ME, Hofman A, Kaplan RC, Kardia SL, Kiel DP, Oostra BA, Orwoll ES, Parimi N, Psaty BM, Rivadeneira F, Rotter JJ, Seshadri S, Singleton A, Tiemeier H, Uitterlinden AG, Zhao W, Bandinelli S, Bennett DA, Ferrucci L, Gudnason V, Harris TB, Karasik D, Launer LJ, Perls TT, Slagboom PE, Tranah GJ, Weir DR, Newman AB, van Duijn CM and Murabito JM. **GWAS of Longevity in CHARGE Consortium Confirms APOE and FOXO3 Candidacy.** *J Gerontol A Biol Sci Med Sci.* 2015;70:110-8.

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DIAGRAM

Type 2 diabetes data were obtained from the DIAGRAM consortium.

International Consortium of Blood Pressure (ICBP)

Blood pressure data were provided by ICBP.

GIANT

BMI data was obtained from the GIANT consortium.

International Genomics of Alzheimer's Project (IGAP)

Alzheimer's disease data were obtained from (IGAP)

Material and methods

International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7 055 881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17 008 Alzheimer's disease cases and 37 154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11 632 SNPs were genotyped and tested for association in an independent set of 8572 Alzheimer's disease cases and 11 312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.

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Psychiatric Genetics Consortium

Schizophrenia, bipolar disorder, major depressive disorder, and ADHD data were obtained from the Psychiatric Genetics Consortium.

Genetic Consortium for Anorexia nervosa

Anorexia nervosa data were obtained from the Genetic Consortium for Anorexia nervosa.

Genetics of Personality Consortium

Neuroticism data were obtained from the Genetics for Personality Consortium.

Tobacco and Genetics Consortium

Data on smoking status were obtained from the Tobacco and Genetics Consortium.

Rheumatoid Arthritis

Rheumatoid arthritis data were obtained from

http://www.broadinstitute.org/ftp/pub/rheumatoid_arthritis/Stahl_etal_2010NG/

Negative Affect

Maciej Trzaskowski and Robert Plomin kindly contributed negative affect data.

NESDA & NTR

Borderline personality data were obtained from NESDA and NTR.

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Supplementary Table 1

Sources of genetic results from genome-wide association consortia.

Phenotype	Consortium	URL	Reference	N GWAS
Coronary Artery Disease Type 2	CARDIoGRA M	http://www.cardiogramplusc4d.org/downloads/	Schunkert et al. Nat Genet 2011; 43: 333-338. PMID: 21378990	22 233 cases 64 controls
diabetes	DIAGRAM	http://diagram-consortium.org/downloads.html	Morris et al. Nat Genet 2012; 44: 981-990. PMID: 22885922	12 171 cases 56 controls
ADHD	Psychiatric Genetics Consortium (PGC)	https://www.med.uconn.edu/pgc/downloads	Cross-Disorder Group of the Psychiatric Genomics Consortium. Lancet 2013; 381: 1371-1379. PMID: 23453885	1947 trio cases 1947 pseudocontrols, 840 cases 688 controls

Alzheimer's disease	International Genomics of Alzheimer's Project (IGAP)	http://www.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php	Lambert et al. Nat Genet 2013; 45: 1452-1458. PMID: 24162737	17 008 cases 37 154 controls
Anorexia nervosa	Genetic Consortium for Anorexia Nervosa (GCAN)	http://www.med.unc.edu/pgc/downloads	Boraska, Vesna, et al. Molecular psychiatry 2014; 19(10): 1085-1094. PMID: 24514567	2907 cases 14860 controls
Bipolar disorder	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/downloads	Psychiatric GWAS Consortium Bipolar Disorder Working Group. Nat Genet 2011; 43: 977-983. PMID: 21926972	7481 cases 9250 controls
Major depressive disorder	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/downloads	Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. Mol Psychiatr 2013; 18: 497-511. PMID: 22472876	9240 cases 9519 controls
Schizophrenia	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/downloads	Schizophrenia Working Group of the Psychiatric Genomics Consortium. Nature 2014; 511: 421-427. PMID: 25056061	36 989 cases 113 075 controls
BMI	GIANT	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Locke et al. Nature 2015; 518: 197-206. PMID: 25673413	339 224
Diastolic blood pressure	International Consortium of Blood Pressure (ICBP)		Ehret et al. (2011) Nature 478, 103-109. PMID: 21909115	69 395
Longevity	CHARGE-Aging and Longevity		Broer et al. J Gerontol A Biol Sci Med Sci 2015; 70: 110-118. PMID: 25199915	6036 cases 3757 controls
Systolic blood pressure	International Consortium of Blood Pressure (ICBP)		Ehret et al. Nature 2011; 478: 103-109. PMID: 21909115	69 395
Neuroticism	Genetics of Personality Consortium	http://www.tweelingerregister.org/GPC/	De Moor et al. JAMA Psychiatry, 72(7): 642-650. PMID: 25993607	63 661
Negative Affect			Trzaskowski et al. PLOS One 2013; 8(4)	2810 cases
Rheumatoid Arthritis	-	http://www.broadinstitute.org/ftp/pub/rheumatoid_arthritis/Stahl_et_al_2010NG/	Stahl et al. Nat Genet 2010; 42:508-14. PMID: 20453842	5539 cases 20 169 controls
Smoking Status	Tobacco and Genetics Consortium	https://www.med.unc.edu/pgc/files/resultfiles/tag.evrsmk.tbl.gz	Tobacco and Genetics Consortium. Nat Genet 2010; 42(5): 441-447. PMID: 20418890	74 053
Borderline Personality	NESDA and NTR		Lubke et al. Mol Psych 2015; 19:923-929. PMID: 23979607	7125

Supplementary Table 2

Associations between polygenic profiles of health related traits, and neuroticism controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values (after False Discovery Rate correction, $P < 0.0065$) are shown in bold.

		Neuroticism				
		Threshold	β	SE	R2	p
Mental health	ADHD	0.01	-0.00287	0.002994	8.26×10^{-6}	0.337012
		0.05	0.004543	0.002994	2.06×10^{-5}	0.129231
		0.1	0.002974	0.002994	8.84×10^{-6}	0.32062
		0.5	0.003187	0.002996	1.01×10^{-5}	0.287361
		1	0.00351	0.002996	1.23×10^{-5}	0.241329
	Alzheimer's Disease	0.01	-0.00139	0.002997	1.92×10^{-6}	0.643781
		0.05	-0.00647	0.003002	4.16×10^{-5}	0.031179
		0.1	-0.00523	0.003004	2.72×10^{-5}	0.081515
		0.5	-0.00022	0.003008	4.70×10^{-8}	0.942228
		1	0.000818	0.003008	6.63×10^{-7}	0.785614
	Anorexia Nervosa	0.01	0.004731	0.002995	2.24×10^{-5}	0.114197
		0.05	0.003593	0.002995	1.29×10^{-5}	0.230219
		0.1	0.005362	0.002996	2.87×10^{-5}	0.073496
		0.5	0.000139	0.003001	1.93×10^{-8}	0.963021
		1	-0.00112	0.00301	1.23×10^{-6}	0.710872
	Bipolar Disorder	0.01	0.012695	0.003	0.00016	2.33×10^{-5}
		0.05	0.015862	0.00301	0.000249	1.37×10^{-7}
		0.1	0.017013	0.003016	0.000285	1.70×10^{-8}
		0.5	0.017078	0.003028	0.000285	1.71×10^{-8}
		1	0.016886	0.003029	0.000278	2.50×10^{-8}
	Borderline Personality	0.01	0.012467	0.002995	0.000155	3.15×10^{-5}
		0.05	0.011175	0.002996	0.000125	0.000192
		0.1	0.01116	0.002997	0.000124	0.000196
		0.5	0.014967	0.002999	0.000223	6.02×10^{-7}
		1	0.015028	0.002999	0.000225	5.43×10^{-7}
	Major Depressive Disorder	0.01	0.017178	0.003003	0.000293	1.07×10^{-8}
		0.05	0.024092	0.003021	0.000569	1.54×10^{-15}
		0.1	0.028489	0.00303	0.000791	5.51×10^{-21}
		0.5	0.034745	0.003051	0.001161	4.92×10^{-30}
		1	0.035716	0.003051	0.001226	1.23×10^{-31}
	Negative affect (anxiety)	0.01	0.004815	0.002994	2.32×10^{-5}	0.107844
		0.05	0.004631	0.002994	2.14×10^{-5}	0.121922
		0.1	0.004652	0.002995	2.16×10^{-5}	0.120399
		0.5	0.008842	0.002997	7.80×10^{-5}	0.003171
		1	0.009487	0.002997	8.98×10^{-5}	0.001546
	Neuroticism (GPC)	0.01	0.026405	0.003	0.0007	1.38×10^{-18}
		0.05	0.033051	0.002995	0.001097	2.66×10^{-28}
		0.1	0.037028	0.002995	0.001376	4.30×10^{-35}
		0.5	0.043349	0.002994	0.001885	1.77×10^{-47}

Physical health	Schizophrenia	1	0.043267	0.002994	0.001877	2.71×10⁻⁴⁷
		0.01	0.029828	0.00302	0.000873	5.32×10⁻²³
		0.05	0.034372	0.003046	0.001139	1.66×10⁻²⁹
		0.1	0.035914	0.003058	0.001234	7.88×10⁻³²
		0.5	0.033529	0.003084	0.001058	1.63×10⁻²⁷
	Blood Pressure: Diastolic	1	0.033817	0.003086	0.001075	6.23×10⁻²⁸
		0.01	0.003944	0.002995	1.55×10 ⁻⁵	0.187925
		0.05	-0.0033	0.002998	1.08×10 ⁻⁵	0.271665
		0.1	-0.00471	0.003002	2.20×10 ⁻⁵	0.116712
		0.5	-0.00294	0.003004	8.60×10 ⁻⁶	0.327081
	Blood Pressure: Systolic	1	-0.00258	0.003003	6.60×10 ⁻⁶	0.39054
		0.01	-0.00157	0.002996	2.45×10 ⁻⁶	0.601327
		0.05	-0.00159	0.002999	2.51×10 ⁻⁶	0.596891
		0.1	-0.00046	0.003	2.12×10 ⁻⁷	0.877804
		0.5	0.000151	0.003005	2.26×10 ⁻⁸	0.959928
	BMI	1	-0.00124	0.003005	1.52×10 ⁻⁶	0.68005
		0.01	-0.00949	0.002995	9.00×10 ⁻⁵	0.001529
		0.05	-0.00857	0.002996	7.33×10 ⁻⁵	0.004219
		0.1	-0.00816	0.002997	6.64×10 ⁻⁵	0.006459
		0.5	-0.0049	0.003	2.39×10 ⁻⁵	0.102193
	Coronary Artery Disease	1	-0.00508	0.003	2.57×10 ⁻⁵	0.090145
		0.01	0.005668	0.002994	3.21×10 ⁻⁵	0.058318
		0.05	0.009317	0.002995	8.67×10 ⁻⁵	0.001866
		0.1	0.010949	0.002995	0.00012	0.000257
		0.5	0.010614	0.002996	0.000112	0.000396
	Longevity	1	0.010072	0.002996	0.000101	0.000776
		0.01	-0.00181	0.003014	3.24×10 ⁻⁶	0.547298
		0.05	-0.00511	0.003028	2.55×10 ⁻⁵	0.091694
		0.1	-0.00093	0.002996	8.72×10 ⁻⁷	0.755097
		0.5	-0.00261	0.003001	6.78×10 ⁻⁶	0.38437
	Rheumatoid Arthritis	1	-0.00217	0.003001	4.68×10 ⁻⁶	0.470043
		0.01	0.000553	0.002998	-5.10E-05	0.853539
		0.05	-0.00065	0.003001	-5.09E-05	0.829678
		0.1	-0.00013	0.003005	-5.13E-05	0.964768
		0.5	-0.00066	0.00302	-5.09E-05	0.826638
	Smoking Status	1	-0.00058	0.003022	-5.10E-05	0.846755
		0.01	0.003084	0.00304	-4.21E-05	0.310425
		0.05	0.014977	0.003084	0.00016	1.20×10⁻⁶
		0.1	0.014199	0.003108	0.000136	4.91×10⁻⁶
		0.5	0.016294	0.003158	0.000187	2.48×10⁻⁷
	Type 2 Diabetes	1	0.01561	0.003164	0.000167	8.11×10⁻⁷
		0.01	-0.00313	0.003014	9.67×10 ⁻⁶	0.298869
		0.05	-0.0015	0.003032	2.21×10 ⁻⁶	0.619643

Physical health	Type 2 Diabetes	0.1	-0.00228	0.003041	5.03×10^{-6}	0.453812
		0.5	0.000433	0.003069	1.78×10^{-7}	0.887774
		1	0.001598	0.00307	2.43×10^{-6}	0.602796

Supplementary Table 3a, Associations between polygenic profiles of health related traits, and neuroticism controlling for age, assessment centre, genotyping batch and array, and ten principal components for population structure stratified by gender. Statistically significant values are shown in bold.

Trait Category	Traits from GWAS consortia	Females (n = 57,074)				Males (n = 50,964)			
		β	r ²	p	β	r ²	p	β	p
Mental health	ADHD	0.0059	3.50E-05	0.1554	0.0031	1.02E-05	0.4675		
	Alzheimer's Disease	-0.0055	3.04E-05	0.1855	-0.0076	5.87E-05	0.0817		
	Anorexia Nervosa	0.0004	1.42E-07	0.9280	0.0108	0.0001	0.0126		
	Bipolar Disorder	0.0152	0.00023	0.0003	0.0193	0.0004	1.06E-05		
	Borderline Personality	0.0146	0.00021	0.0005	0.0156	0.0003	2.78E-04		
	Major Depressive Disorder	0.0373	0.00134	1.54E-18	0.0340	0.0012	1.04E-14		
	Negative Affect (anxiety)	0.0112	0.00013	0.0065	0.0074	5.65E-05	0.0877		
	Neuroticism (GPC)	0.0448	0.00197	5.29E-27	0.0417	0.0017	3.59E-22		
	Schizophrenia	0.0309	0.00092	3.44E-13	0.0417	0.0017	3.23E-21		
Physical health	Blood Pressure: Diastolic	-0.0091	8.26E-05	0.0290	4.68E-05	2.28E-09	0.9914		
	Blood Pressure: Systolic	-0.0059	3.49E-05	0.1556	0.0032	1.07E-05	0.4584		
	BMI	-0.0070	4.87E-05	0.0939	-0.0123	0.0002	0.0043		
	Coronary Artery Disease	0.0117	0.00014	0.0048	0.0100	0.0001	0.0212		
	Longevity	-0.0051	2.59E-05	0.2214	-0.0051	2.65E-05	0.2424		
	Rheumatoid Arthritis	0.0001	-6.99E-05	0.9734	-0.0016	2.71E-05	0.7071		
	Smoking Status	0.0211	3.31E-04	1.53E-06	0.0107	1.32E-04	0.0183		
	Type 2 Diabetes	0.0010	9.47E-07	0.8152	-0.0077	6.08E-05	0.0765		

Supplementary Table 3b, Associations between polygenic profiles of health related traits, and neuroticism controlling for sex, assessment centre, genotyping batch and array, and ten principal components for population structure stratified by age (under and over 60 years). Statistically significant values are shown in bold.

Trait Category	Traits from GWAS consortia	Under 60 years (n = 65 337)			Over 60 years (n = 42 701)		
		β	r^2	p	β	r^2	p
Mental health	ADHD	0.0058	3.26E-05	0.1403	0.0033	1.2E-05	0.4648
	Alzheimer's Disease	-0.0067	4.30E-05	0.0905	-0.0065	4.6E-05	0.1561
	Anorexia Nervosa	0.0041	1.57E-05	0.3057	0.0072	5.7E-05	0.1154
	Bipolar Disorder	0.0205	0.0004	3.12E-07	0.0119	0.0002	0.0097
	Borderline Personality	0.0164	0.0003	3.77E-05	0.0132	0.0002	0.0036
	Major Depressive Disorder	0.0390	0.0014	4.59E-22	0.0315	0.0011	1.1E-11
	Negative Affect (anxiety)	0.0144	0.0002	0.0003	0.0024	6.2E-06	0.6024
	Neuroticism (GPC)	0.0440	0.0019	9.81E-29	0.0425	0.0020	1.7E-20
	Schizophrenia	0.0385	0.0014	2.17E-21	0.0324	0.0011	3.2E-12
Physical health	Blood Pressure: Diastolic	-0.0006	3.17E-07	0.8844	-0.0117	0.0001	0.01061
	Blood Pressure: Systolic	0.0016	2.33E-06	0.6934	-0.0068	5.2E-05	0.1338
	BMI	-0.0104	0.0001	0.0087	-0.0081	7.2E-05	0.0768
	Coronary Artery Disease	0.0094	8.34E-05	0.0184	0.0135	0.0002	0.0029
	Longevity	-0.0064	3.84E-05	0.1096	-0.0036	1.4E-05	0.4321
	Rheumatoid Arthritis	-0.0008	-4.64E-05	0.8382	5.63E-04	5.5E-06	0.9027
	Smoking Status	0.0180	2.34E-04	1.53E-05	1.35E-02	0.0002	0.0051
	Type 2 Diabetes	-0.0021	4.31E-06	0.5918	-0.0043	2.1E-05	0.3442

Supplementary Table 3c. Associations between polygenic profiles of health related traits, and neuroticism controlling for assessment centre, genotyping batch and array, and ten principal components for population structure stratified by gender and age (females under and over 60 years). Statistically significant values are shown in bold.

Trait Category	Traits from GWAS consortia	Females under 60 (n = 35 774)				Females over 60 (n = 21 300)			
		β	r ²	p		β	r ²	p	
Mental health	ADHD	0.0060	3.58E-05	0.2576		0.0065	4.56E-05	0.3239	
	Alzheimer's Disease	-0.0043	1.80E-05	0.4224		-0.0081	7.3E-05	0.2122	
	Anorexia Nervosa	-0.0013	1.59E-06	0.8112		0.0035	1.28E-05	0.6016	
	Bipolar Disorder	0.0210	0.0004	0.0001		0.0052	2.89E-05	0.4325	
	Borderline Personality	0.0140	0.0002	0.0097		0.0157	0.000267243	0.0170	
	Major Depressive Disorder	0.0396	0.0015	5.09E-13		0.0351	0.0013	1.64E-07	
	Negative Affect (anxiety)	0.0192	0.0004	0.0003		-0.0016	2.57E-06	0.8149	
	Neuroticism (GPC)	0.0435	0.0019	4.10E-16		0.0463	0.0023	3.23E-12	
	Schizophrenia	0.0335	0.0010	9.79E-10		0.0276	0.0008	3.81E-05	
Physical health	Blood Pressure: Diastolic	-0.0038	1.38E-05	0.4814		-0.0195	0.0004	0.0031	
	Blood Pressure: Systolic	-0.0025	6.07E-06	0.6412		-0.0121	0.0002	0.0659	
	BMI	-0.0040	1.53E-05	0.4596		-0.0109	0.0001	0.0999	
	Coronary Artery Disease	0.0112	0.0001	0.0361		0.0113	0.0001	0.0846	
	Longevity	-0.0065	4.02E-05	0.2305		-0.0038	1.49E-05	0.5734	
	Rheumatoid Arthritis	0.0035	7.98E-06	0.5140		-0.0040	8.23E-06	0.5435	
	Smoking Status	0.0244	5.05E-04	1.48E-05		0.0156	0.0002	0.0251	
	Type 2 Diabetes	-0.0024	5.54E-06	0.6560		0.0072	5.65E-05	0.2723	

Supplementary Table 3c. Associations between polygenic profiles of health related traits, and neuroticism controlling for assessment centre, genotyping batch and array, and ten principal components for population structure stratified by gender and age (males under and over 60 years). Statistically significant values are shown in bold.

Trait Category	Traits from GWAS consortia	Males under 60 years (n = 29,563)				Males over 60 years (n = 21,401)			
		β	r ²	p		β	r ²	p	
Mental health	ADHD	0.0057	3.15E-05	0.3348		0.0005	2.99E-07	0.9363	
	Alzheimer's Disease	-0.0098	9.28E-05	0.0976		-0.0048	2.68E-05	0.4487	
	Anorexia Nervosa	0.0106	0.0001	0.0730		0.0105	0.0001	0.0937	
	Bipolar Disorder	0.0200	0.0004	0.0008		0.0191	0.0004	0.0028	
	Borderline Personality	0.0194	0.0004	0.0010		0.0110	0.0001	0.0811	
	Major Depressive Disorder	0.0385	0.0014	1.28E-10		0.0280	0.0009	1.36E-05	
	Negative Affect (anxiety)	0.0083	6.64E-05	0.1612		0.0065	4.79E-05	0.3111	
	Neuroticism (de Moor, 2015)	0.0446	0.0019	3.31E-14		0.0388	0.0017	7.70E-10	
	Schizophrenia	0.0448	0.0019	1.17E-13		0.0372	0.0016	6.73E-09	
Physical health	Blood Pressure: Diastolic	0.0032	1.01E-05	0.5853		-0.0044	2.30E-05	0.4830	
	Blood Pressure: Systolic	0.0065	4.12E-05	0.2699		-0.0019	4.03E-06	0.7689	
	BMI	-0.0180	0.0003	0.0021		-0.0053	3.22E-05	0.4062	
	Coronary Artery Disease	0.0070	4.68E-05	0.2394		0.0156	0.0003	0.0135	
	Longevity	-0.0062	3.71E-05	0.2946		-0.0037	1.56E-05	0.5629	
	Rheumatoid Arthritis	-0.0059	3.16E-05	0.3174		0.0051	3.93E-05	0.4254	
	Smoking Status	0.0101	8.79E-05	0.1027		0.0117	1.51E-04	0.0815	
	Type 2 Diabetes	-0.0018	3.03E-06	0.7647		-0.0158	0.0003	0.0132	

Appendix 5. Supplementary material to Section 7.2

Deary and Hagenaars et al. Genetic contributions to self-reported tiredness

Supplementary Materials for:

Genetic contributions to self-reported tiredness/energy.

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Phenotypic measures

Grip strength

Right and left hand grip strength were measured using a Jamar J00105 hydraulic hand dynamometer. A dominant grip strength measure was computed based on handedness.

Forced expiratory volume in 1s

Forced expiratory volume in one second was measured using a Vitalograph Pneumotrac 6800. Each participant was asked to record two to five blows, lasting for a minimum of six seconds, within a period of six minutes. The reproducibility of the first two blows was compared and if there was less than 5% difference in forced volume vital capacity and forced expiratory volume in one second, a third blow was not required.

Height

Standing height was measured in cm using a Seca 202 device.

BMI

BMI values in kg/m² were constructed from height and weight measures.

Self-rated health

Participants were asked the question, “In general how would you rate your overall health?”. Possible answers were “Excellent/Good/Fair/Poor/Do not know/Prefer not to answer”. We created a four-category SRH variable indexing how each participant rated their health ranging from “excellent” to “poor”; excluding those that responded with “do not know” or “prefer not to answer”. A higher score for SRH indicates a better health rating (Harris et al., 2015).

Verbal-numerical reasoning

Verbal-numerical reasoning was measured by a thirteen item-test with a time limit of two minutes, completed by 36 035 individuals. Six items were verbal and seven numerical. An example of a verbal question is ‘Bud is to flower as child is to?’ (Possible answers: ‘Grow/Develop/Improve/Adult/Old/Do not know/Prefer not to answer’). An example of a numerical question is ‘If sixty is more than half of seventy-five, multiply twenty-three by three. If not subtract 15 from eighty-five. Is the answer?’ (Possible answers: ‘68/69/70/71/72/Do not know/Prefer not to answer’). The verbal-numerical reasoning score was the total score out of thirteen (Hagenaars et al., 2016).

Neuroticism

Participants completed 12 questions of the Eysenck Personality Questionnaire-Revised Short Form (EPQ-R Short Form) neuroticism scale (Deary & Bedford, 2011; Eysenck, Eysenck, & Barrett, 1985). Neuroticism refers to the relatively stable personality trait that assesses individual differences in the tendency to experience negative emotions. A summary score was derived to obtain a measure of neuroticism (Gale et al., In Press).

Sources of genetic results from genome-wide association consortia

CARDIoGRAM

Coronary artery disease data have been contributed by CARDIoGRAMplusC4D investigators.

CHARGE-Aging and Longevity

Longevity data have been provided by the CHARGE-Aging and Longevity consortium. Longevity was defined as reaching age 90 years or older. Genotyped participants who died between the ages of 55 and 80 years were used as the control group. There were 6036 participants who achieved longevity and 3757 participants in the control group across participating studies in the discovery meta-analysis.

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CHARGE-Inflammation Working Group

C-reactive protein data have been provided by the CHARGE-Inflammation Working Group.

Abbas Dehghan, Josée Dupuis, Maja Barbalic, Joshua C. Bis, Gudny Eiriksdottir, Chen Lu, Niina Pellikka, Henri Wallaschofski, Johannes Kettunen, Peter Henneman, Jens Baumert, David P. Strachan, Christian Fuchsberger, Veronique Vitart, James F. Wilson, Guillaume Paré, Silvia Naitza, Megan E. Rudock, Ida Surakka, Eco J.C. de Geus, Behrooz Z. Alizadeh, Jack Guralnik, Alan Shuldiner, Toshiko Tanaka, Robert Y.L. Zee, Renate B. Schnabel, Vijay Nambi, Maryam Kavousi, Samuli Ripatti, Matthias Nauck, Nicholas L. Smith, Albert V. Smith, Jouko Sundvall, Paul Scheet, Yongmei Liu, Aimo Ruokonen, Lynda M. Rose, Martin G. Larson, Ron C. Hoogeveen, Nelson B. Freimer, Alexander Teumer, Russell P. Tracy, Lenore J. Launer, Julie E. Buring, Jennifer F. Yamamoto, Aaron R. Folsom, Eric J.G. Sijbrands, James Pankow, Paul Elliott, John F. Keaney, Wei Sun, Antti-Pekka Sarin, João D. Fontes, Sunita Badola, Brad C. Astor, Albert Hofman, Anneli Pouta, Karl Werdan, Karin H. Greiser, Oliver Kuss, Henriette E. Meyer zu Schwabedissen, Joachim Thiery, Yalda Jamshidi, Ilja M. Nolte, Nicole Soranzo, Timothy D. Spector, Henry Völzke, Alexander N. Parker, Thor Aspelund, David Bates, Lauren Young, Kim Tsui, David S. Siscovick, Xiuqing Guo, Jerome I. Rotter, Manuela Uda, David Schlessinger, Igor Rudan, Andrew A. Hicks, Brenda W. Penninx, Barbara Thorand, Christian Gieger, Joe Coresh, Gonneke Willemsen, Tamara B. Harris, Andre G. Uitterlinden, Marjo-Riitta Järvelin, Kenneth Rice, Dörte Radke, Veikko Salomaa, Ko Willems van Dijk, Eric Boerwinkle, Ramachandran S. Vasan, Luigi Ferrucci, Quince D. Gibson, Stefania Bandinelli, Harold Snieder, Dorret I. Boomsma, Xiangjun Xiao, Harry Campbell, Caroline Hayward, Peter P. Pramstaller, Cornelia M. van Duijn, Leena Peltonen, Bruce M. Psaty, Vilmundur Gudnason, Paul M. Ridker, Georg Homuth, Wolfgang Koenig, Christie M. Ballantyne, Jacqueline C.M. Witteman, Emelia J. Benjamin, Markus Perola and Daniel I. Chasman. **Meta-Analysis of Genome-Wide Association Studies in >80 000 Subjects Identifies Multiple Loci for C-Reactive Protein Levels.** *Circulation* 2011; 123: 731-738.

Acknowledgments

The CHARGE Inflammation Working Group analysis of C-reactive protein was funded through the individual contributing studies. The working group thanks all study participants and study staff.

CHIC

Childhood cognitive ability data were obtained from the CHIC consortium.

DIAGRAM

Type 2 diabetes data were obtained from the DIAGRAM consortium.

Genetic Consortium for Anorexia nervosa

Anorexia nervosa data were obtained from the Genetic Consortium for Anorexia nervosa.

Global Lipids Consortium

LDL cholesterol, HDL cholesterol and triglycerides data have been contributed by the Global Lipids Consortium.

GIANT

BMI, height, waist-hip ratio and obesity data were obtained from the GIANT consortium.

International Consortium for Blood Pressure (ICBP)

Blood pressure data were provided by ICBP.

International Genomics of Alzheimer's Project (IGAP)

Alzheimer's disease data were obtained from (IGAP)

Material and methods

International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7 055 881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17 008 Alzheimer's disease cases and 37 154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11 632 SNPs were genotyped and tested for association in an independent set of 8572 Alzheimer's disease cases and 11 312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.

Acknowledgments

We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results data for these analyses. The investigators within IGAP contributed to the design and implementation of IGAP and/or provided data but did not participate in analysis or writing of this report. IGAP was made possible by the generous participation of the control subjects, the patients, and their families. The i-Select chips was funded by the French National Foundation on Alzheimer's disease and related disorders. EADI was supported by the LABEX (laboratory of excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille, Université de Lille 2 and the Lille University Hospital. GERAD was supported by the Medical Research Council (Grant n° 503480), Alzheimer's Research UK (Grant n° 503176), the Wellcome Trust (Grant n° 082604/2/07/Z) and German Federal Ministry of Education and Research (BMBF): Competence Network Dementia (CND) grant n° 01GI0102, 01GI0711, 01GI0420. CHARGE was partly supported by the NIH/NIA grant R01 AG033193 and the NIA AG081220 and AGES contract N01-AG-12100, the NHLBI grant R01 HL105756, the Icelandic Heart Association, and the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association grant ADGC-10-196728.

MAGIC

Data on glycaemic traits have been contributed by MAGIC investigators.

Psychiatric Genetics Consortium

Schizophrenia, bipolar disorder, major depressive disorder and ADHD and autism data were obtained from the Psychiatric Genetics Consortium.

Rheumatoid Arthritis

Rheumatoid arthritis data were obtained from the Broad Institute

SpiroMeta/CHARGE Pulmonary

Lung function data were obtained from the SpiroMeta and CHARGE Pulmonary group.

Tobacco and Genetic Consortium

Smoking status data were obtained from the Tobacco and Genetics Consortium.

The Genetics of Personality Consortium

Neuroticism data were obtained from the Genetics of Personality consortium.

Stratified linkage disequilibrium score regression

The summary statistics from the GWAS on tiredness/little energy were portioned into functional categories using the same data processing pipeline as Finucane et al., (Finucane et al., 2015).

The heritability Z-score for the tiredness/little energy phenotype was 9.84 indicating a sufficient level of polygenic signal for use with stratified LD score regression. We first derive the heritability for each of the functional annotations whilst controlling for LD and for the level of overlap between the functional annotations used. Using the heritability of each of the functional annotations we then derive an enrichment metric defined as $\Pr(h^2)/\Pr(\text{SNPs})$, or the proportion of the heritability, over the proportion of SNPs found in the annotation. This describes the degree to which the annotation is enriched for variants that are associated with tiredness/little energy. LD scores were calculated using the European samples from the 1000 Genomes project (1000G) and only included the HapMap 3 SNPs with a minor allele frequency (MAF) of >0.05 . For controlling for multiple testing a False discovery rate (FDR) (Benjamini & Hochberg, 1995) was applied to the full baseline model (52 tests). For the tissue specific analysis, 10 tests were controlled for using FDR correction.

Sensitivity analyses

Sensitivity analyses were performed by excluding individuals with a diagnosis for type 2 diabetes ($n = 725$) from the regression models between tiredness and polygenic risk for type 2 diabetes. The diagnosis for type 2 diabetes was based on a verbal interview with a nurse, which followed after a touchscreen questionnaire asking about history of illnesses. If a participant had answered in the touchscreen questionnaire that they had diabetes (any type) the nurse would confirm this and amend if incorrectly answered in the touchscreen questionnaire. Sensitivity analysis for major depressive disorder were performed in a different way. When excluding individuals with a probable diagnosis of major depressive disorder, based on the criteria by (Smith et al., 2013), individuals with missing data on the mood questions are not considered, even though they might have diagnosis of major depressive disorder. Therefore, all polygenic profile analysis were rerun in individuals with sufficient information to make a probable diagnosis of major depressive disorder ($N = 31\,523$), followed by excluding individuals with a probable diagnosis of major depressive disorder ($N = 7364$) from this full set.

Supplementary Table 1

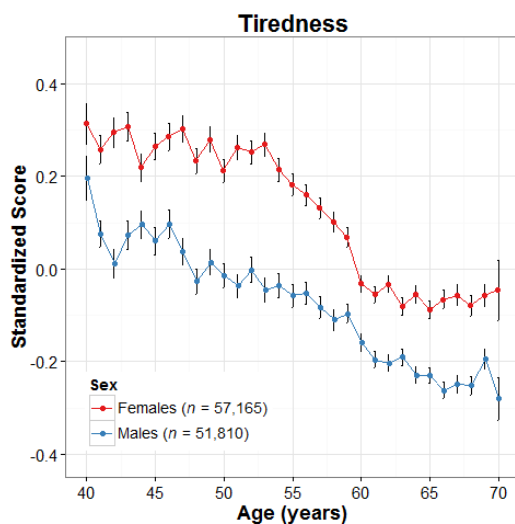
Sources of genetic results from genome-wide association consortia

Phenotype	Consortium	URL	Reference	No. of individuals in GWAS
Childhood cognitive ability	CHIC	http://ssgac.org/Data.php	Benyamin et al. Mol Psychiatry 2014; 19: 253-258. PMID: 23358156	17 989
Neuroticism	The Genetics of Personality Consortium	http://www.tweelingenregister.org/GPC/	De Moor, et al. JAMA Psychiatry 2015; 72(7):642-650. PMID: 25993607	63 661
BMI	GIANT	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Locke et al. Nature 2015; 518: 197-206. PMID: 25673413	339 224
Height	GIANT	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Wood et al. Nature Genetics 2014; 11:1173-86	253 288
Obesity	GIANT	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Berndt et al. Nature Genetics 2013; 45:501-512	263 407
Waist-hip ratio	GIANT	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Shungin et al. Nature 2015; 518: 187-196	224 459
Longevity	CHARGE-Aging and Longevity working group		Broer et al. J Gerontol A Biol Sci Med Sci 2015; 70: 110-118. PMID: 25199915	6036 cases 3757 controls
ADHD	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/downloads	Cross-Disorder Group of the Psychiatric Genomics Consortium. Lancet 2013; 381: 1371-1379. PMID: 23453885	1947 trio cases 1947 trio pseudocases 840 cases 688 controls
Alzheimer's disease	International Genomics of Alzheimer's Project (IGAP)	http://www.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php	Lambert et al. Nat Genet 2013; 45: 1452-1458. PMID: 24162737	17 008 cases 37 154 controls

Autism	Psychiatric Consortium (PGC)	Genetics	http://www.med.unc.edu/pgc/downloads	Cross-Disorder Group of the Psychiatric Consortium. Nat Genet 2013; 45: 984-994. PMID: 23933821	3303 cases 3428 controls
Anorexia nervosa	Genetic Consortium for Anorexia Nervosa (GCAN)	Genetics	http://www.med.unc.edu/pgc/downloads	Boraska, Vesna, et al. Molecular psychiatry 2014; 19(10): 1085-1094. PMID: 24514567	2907 cases 14860 controls
Bipolar disorder	Psychiatric Consortium (PGC)	Genetics	https://www.med.unc.edu/pgc/downloads	Psychiatric GWAS Consortium Bipolar Disorder Working Group. Nat Genet 2011; 43: 977-983. PMID: 21926972	7481 cases 9250 controls
Major depressive disorder	Psychiatric Consortium (PGC)	Genetics	https://www.med.unc.edu/pgc/downloads	Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. Mol Psychiatr 2013; 18: 497-511. PMID: 22472876	9240 cases 9519 controls
Schizophrenia	Psychiatric Consortium (PGC)	Genetics	https://www.med.unc.edu/pgc/downloads	Schizophrenia Working Group of the Psychiatric Genomics Consortium. Nature 2014; 511: 421-427. PMID: 25056061	36 989 cases 113 075 controls
Rheumatoid Arthritis			http://www.broadinstitute.org/ftp/pub/rheumatoid_arthritis/Stahl_et_al_2010NG/	Stahl et al Nature Genetics 2012; 44:483-489	5500 cases 20 000 controls
Forced expiratory volume in 1 second (FEV ₁)	SpiroMeta/CHARGE-Pulmonary			Soler Artigas et al. Nature Genetics 2011; 43: 1082-1090. PMID: 21946350	48 201 controls
Blood pressure: Diastolic	International Consortium of Blood Pressure (ICBP)			Ehret et al. (2011) Nature 478, 103-109. PMID: 21909115	69 395
Blood pressure: Systolic	International Consortium of Blood Pressure (ICBP)			Ehret et al. Nature 2011; 478: 103-109. PMID: 21909115	69 395
HbA1c	MAGIC		http://www.magicinvestigators.org/downloads/	Soranzo et al. Diabetes 2010; 59: 3229-3239	46 368

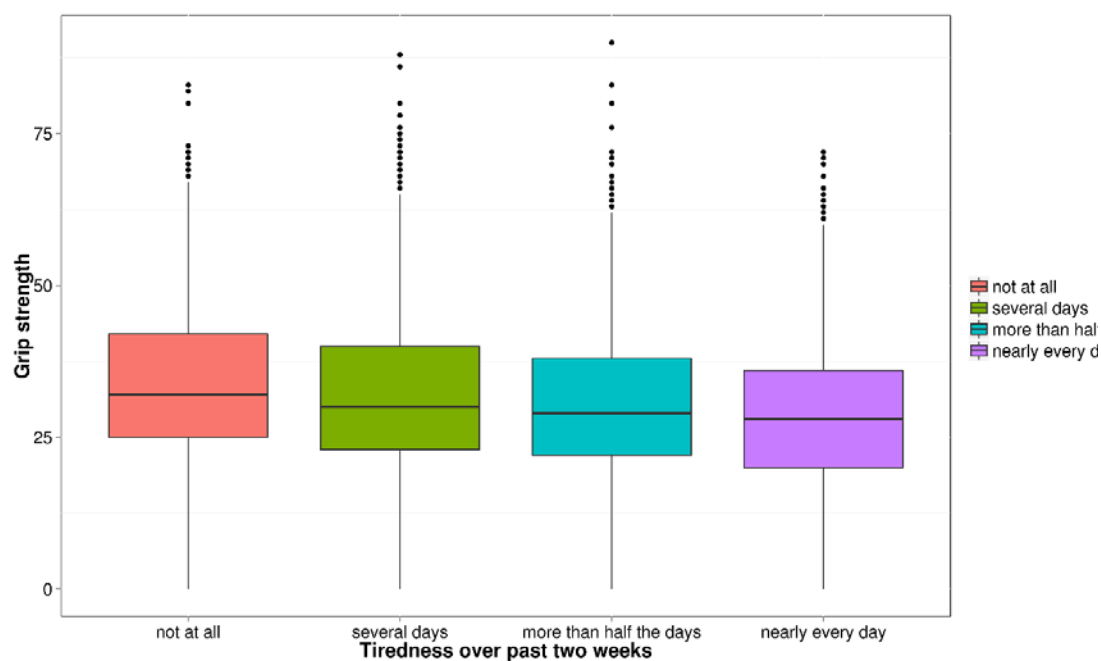
Coronary Artery Disease	CARDIoGRAM	http://www.cardiogramplusc4d.org/downloads/	Schunkert et al. Nat Genet 2011; 43: 333-338. PMID: 21378990	22 cases 64 controls	233
HDL Cholesterol	Global Consortium	http://csg.sph.umich.edu/abecasis/public/lipid/s2013/	Willer et al. Nature Genet 2013; 45: 1274-1283	188	577
LDL Cholesterol	Global Consortium	http://csg.sph.umich.edu/abecasis/public/lipid/s2013/	Willer et al. Nature Genet 2013; 45: 1274-1283	188	577
Triglycerides	Global Consortium	http://csg.sph.umich.edu/abecasis/public/lipid/s2013/	Willer et al. Nature Genet 2013; 45: 1274-1283	188	577
Smoking status	TAG	https://www.med.unc.edu/pgc/files/resultfiles/tag.evrsnk.tbl.gz	Furberg et al Nature Genetics 2010; 42: 441-447	74	053
Type 2 diabetes	DIAGRAM	http://diagram-consortium.org/downloads.html	Morris et al. Nat Genet 2012; 44: 981-990. PMID: 22885922	12 cases 56 controls	171
C-reactive protein	CHARGE Inflammation Group		Dehghan et al. Circulation 2011; 123: 731-738. PMID: 21300955	66	185

Supplementary Figure 1. Age- and sex distribution of standardized tiredness scores

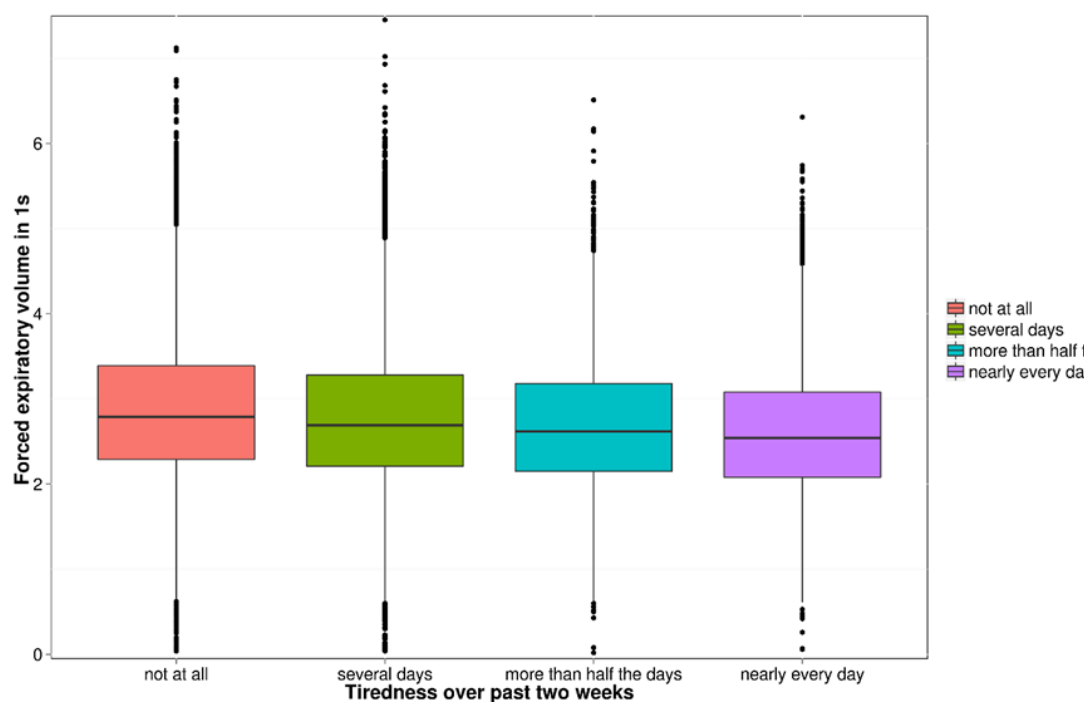


Supplementary Table 2. Frequency table for tiredness and self-rated health

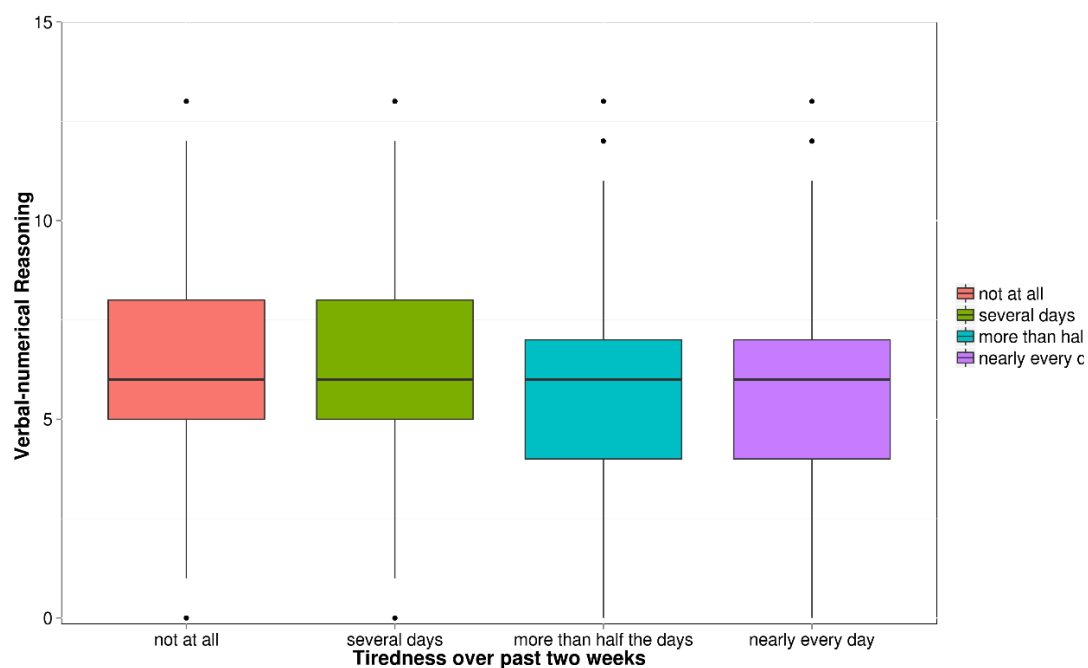
		Self-rated health			
		excellent	good	fair	poor
Tiredness	not at all	12556	32258	6105	428
	several days	4857	25633	11665	1921
	more than half the days	316	2814	2531	695
	nearly every day	215	2000	2710	1944



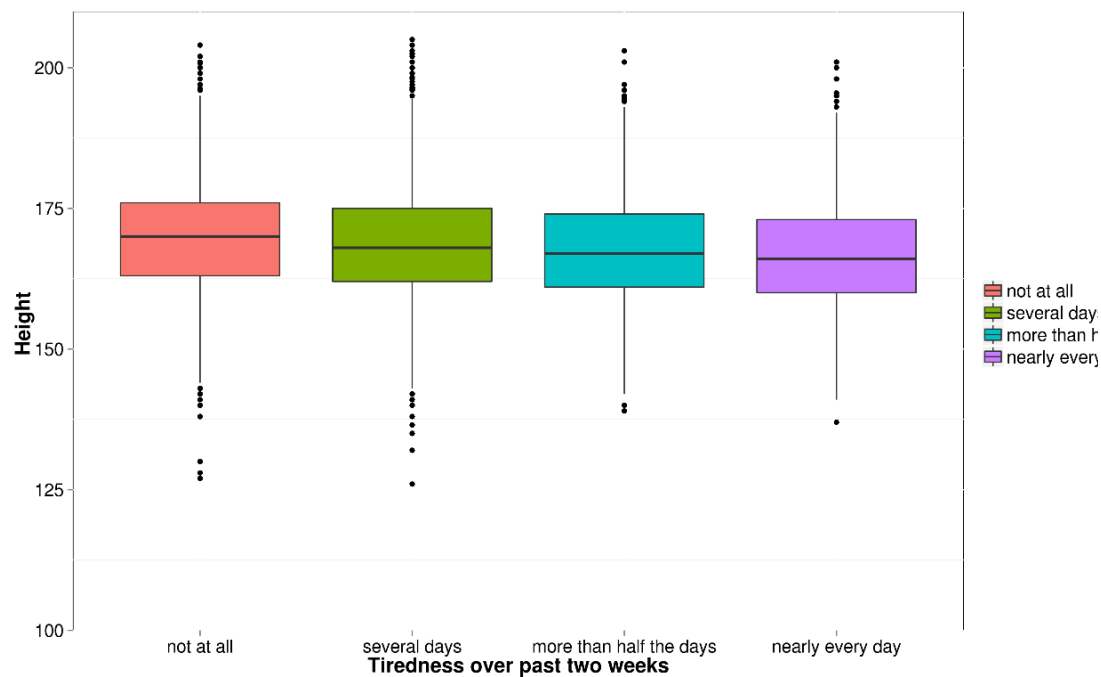
Supplementary Figure 2a. Barplot showing the distribution of grip strength for each category of tiredness.



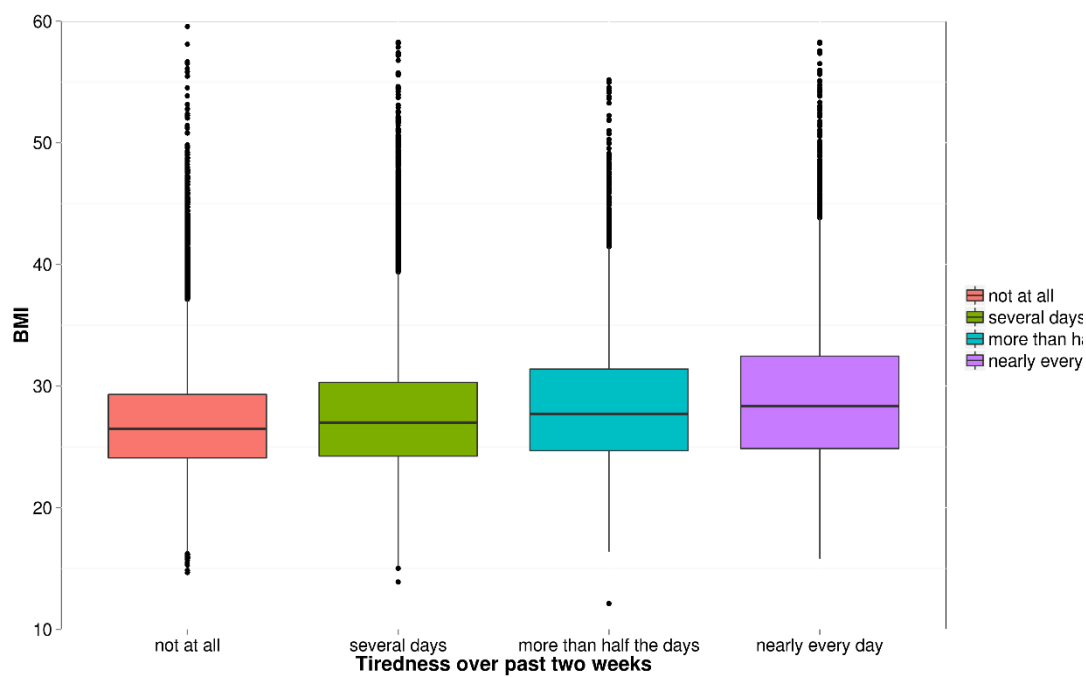
Supplementary Figure 2b. Barplot showing the distribution of lung function for each category of tiredness, 13 individuals with values above 7.5 litres/second have been excluded.



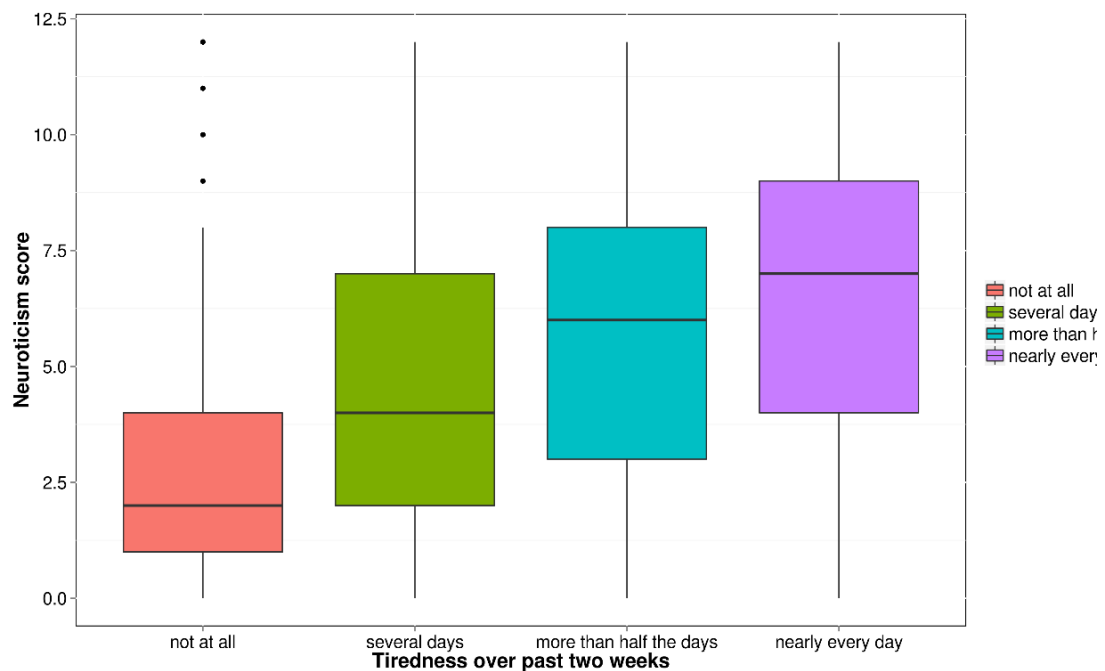
Supplementary Figure 2c. Barplot showing the distribution of verbal-numerical reasoning for each category of tiredness



Supplementary Figure 2d. Barplot showing the distribution of height for each category of tiredness.



Supplementary Figure 2e Barplot showing the distribution of BMI for each category of tiredness.



Supplementary Figure 2f. Barplot showing the distribution of neuroticism for each category of tiredness.

Supplementary Table 3. Gene based analysis conducted on tiredness using MAGMA. Genome-wide significant gene-based hits ($P < 2.8 \times 10^{-6}$) are shown in bold. NSNPS is the number of SNPs in the gene; Effect Size is the number of independent SNPs in the gene.

(See Supplementary Tables at the following URL:

<http://www.nature.com/mp/journal/vaop/ncurrent/suppinf/mp20175s1.html?url=/mp/journal/vaop/ncurrent/full/mp20175a.html>)

Supplementary Table 4. Associations between polygenic profiles of health related traits, and tiredness controlling for age, sex, assessment centre, genotyping batch and array, and ten principal components for population structure. Statistically significant values ($P < 0.0255$) are shown in bold.

(See Supplementary Tables at the following URL:

<http://www.nature.com/mp/journal/vaop/ncurrent/suppinf/mp20175s1.html?url=/mp/journal/vaop/ncurrent/full/mp20175a.html>)

Supplementary Table 5. Associations between polygenic profiles of health-related traits created from GWAS consortia summary data, and the UK Biobank tiredness phenotype controlling for age, sex, assessment centre, genotyping batch and array and 10 principal components for population structure. SRH models are adjusted for self-rated health; N models are adjusted for neuroticism.

(See Supplementary Tables at the following URL:

<http://www.nature.com/mp/journal/vaop/ncurrent/suppinf/mp20175s1.html?url=/mp/journal/vaop/ncurrent/full/mp20175a.html>)

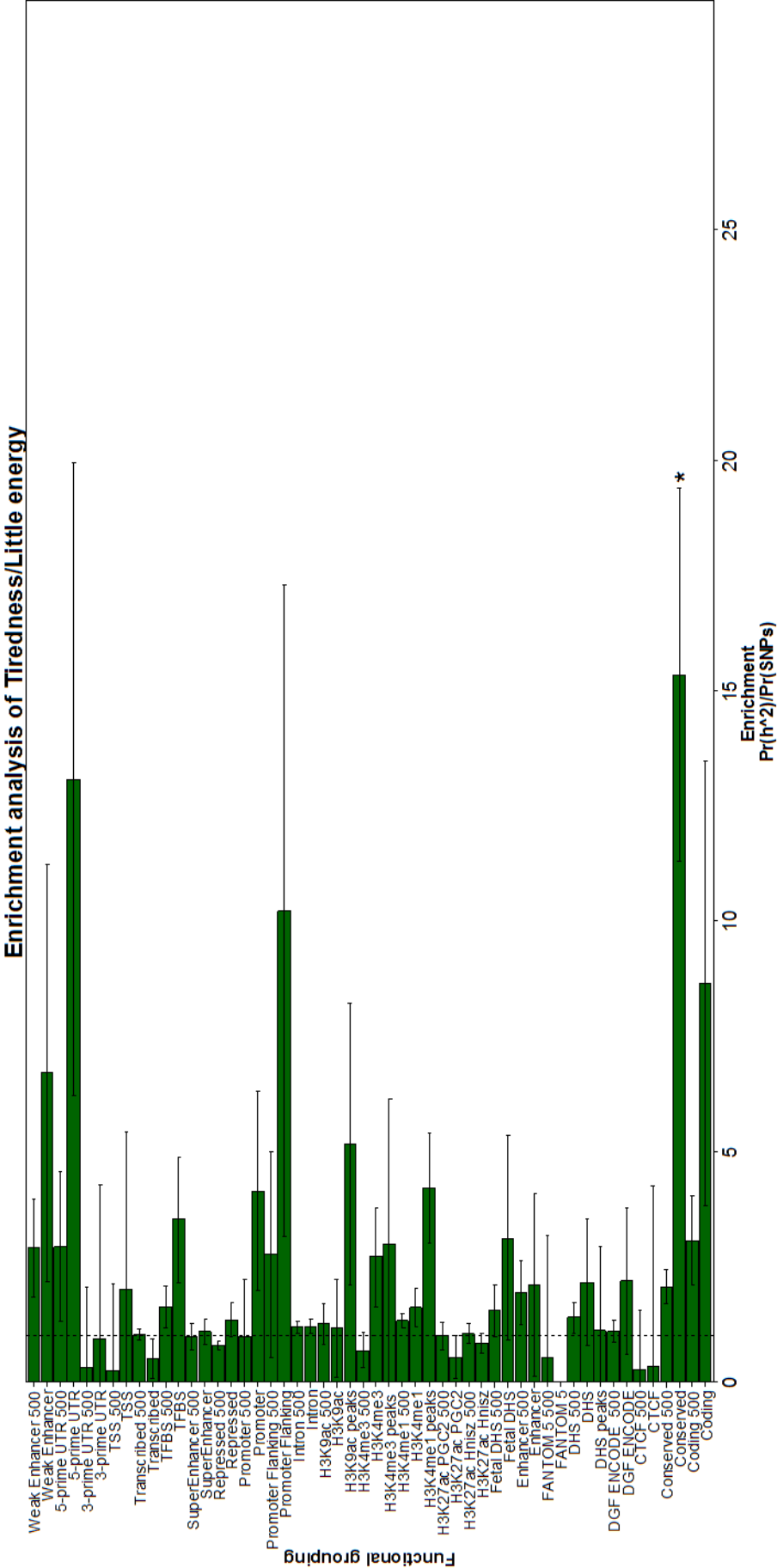
Supplementary Table 6. Associations between polygenic profiles of health-related traits created from GWAS consortia summary data, and the UK Biobank tiredness phenotype controlling for age, sex, assessment centre, genotyping batch and array and 10 principal components for population structure in a subset of individuals who have sufficient data for MDD diagnosis.

(See Supplementary Tables at the following URL:

<http://www.nature.com/mp/journal/vaop/ncurrent/suppinf/mp20175s1.html?url=/mp/journal/vaop/ncurrent/full/mp20175a.html>)

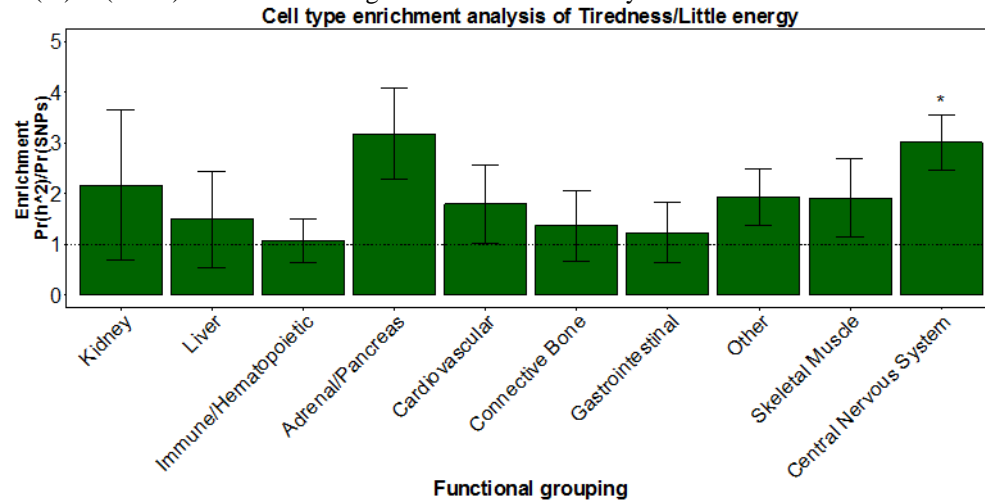
Supplementary Figure 3

Enrichment analysis for tiredness using the 52 functional categories in the baseline model. The enrichment statistic is the proportion of heritability found in each functional group divided by the proportion of SNPs in each group ($\Pr(h^2)/\Pr(\text{SNPs})$). The dashed line indicates no enrichment found when $\Pr(h^2)/\Pr(\text{SNPs}) = 1$. Statistical significance is indicated by asterisk at $P = 0.00039$.



Supplementary Figure 4

Enrichment analysis for tiredness using the 10 cell specific functional categories. The enrichment statistic is the proportion of heritability found in each functional group divided by the proportion of SNPs in each group ($\text{Pr}(h^2)/\text{Pr}(\text{SNPs})$). The dashed line indicates no enrichment found when $\text{Pr}(h^2)/\text{Pr}(\text{SNPs}) = 1$. Statistical significance is indicated by asterisk at $P = 0.000202877$.



Supplementary Table 7. Multivariate model predicting tiredness, including all significant polygenic profile scores together with covariates (age, sex, assessment centre, genotyping batch and array, and ten genetic principal components for population structure; covariate values not shown here). Adjusted R^2 values refer to the polygenic profile scores only (excluding variance explained by the covariates). Statistically significant p-values (after FDR correction; threshold: $P < 0.0243$) are shown in bold.

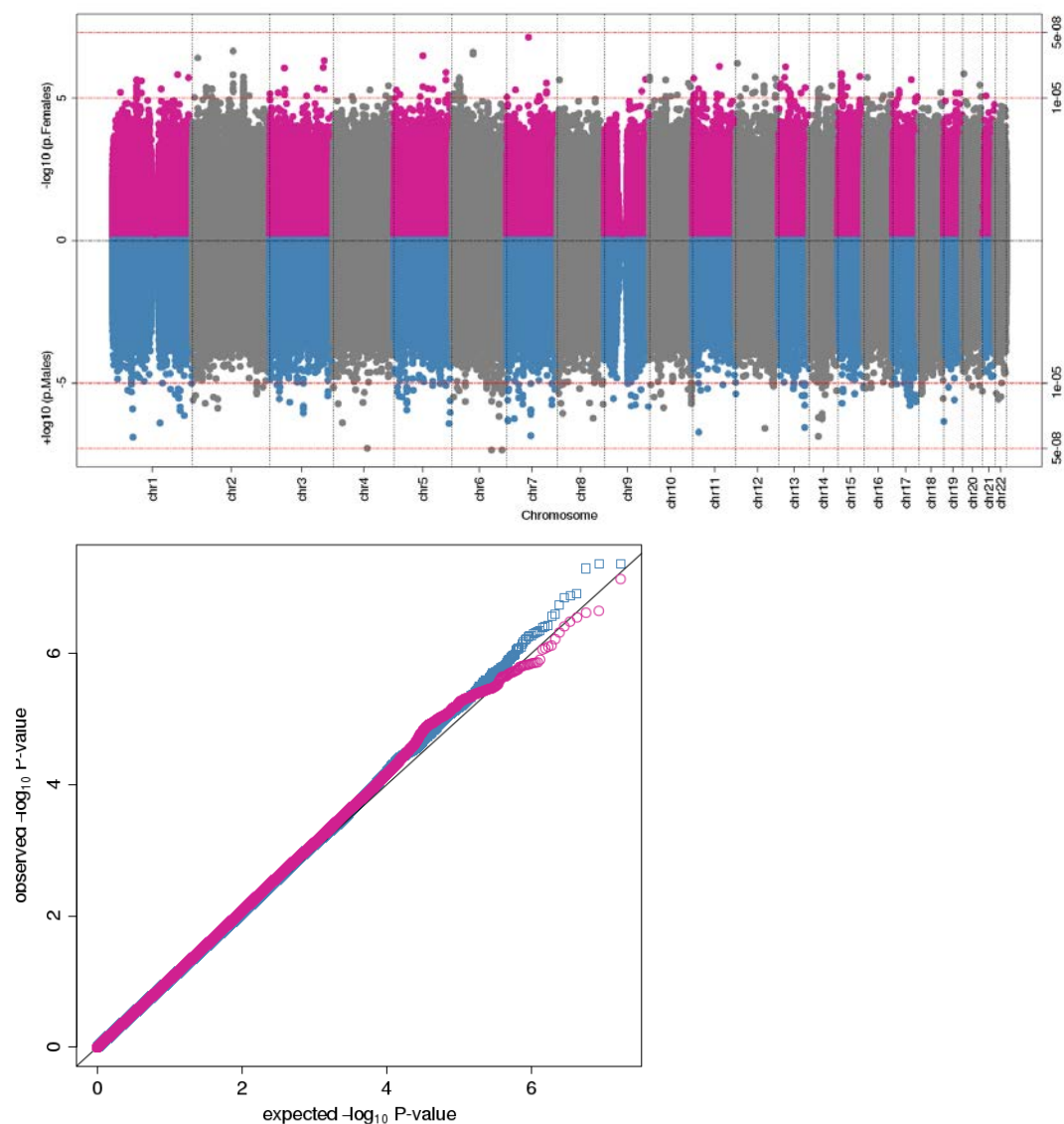
All Traits Adjusted $R^2 = 0.25\%$		
Traits	β	P
BMI	0.0164	0.0001
Cholesterol: HDL	-0.0079	0.0169
Cholesterol: LDL	0.0025	0.4304
Coronary artery disease	0.0045	0.1437
C-reactive protein	0.0032	0.3114
HbA1c	0.0060	0.0537
Height	-0.0015	0.6512
Obesity	0.0057	0.1773
Smoking status	0.0062	0.0527
Triglycerides	0.0097	0.0043
Type 2 diabetes	0.0051	0.1085
Waist-hip ratio	0.0111	0.0011
Bipolar disorder	0.0020	0.5131
Childhood cognitive ability	-0.0073	0.0182
Major depressive disorder	0.0140	8.67×10^{-6}
Neuroticism	0.0145	1.92×10^{-6}
Schizophrenia	0.0254	2.25×10^{-15}

Supplementary Table 8. Genetic correlations between allostatic load variables. Statistically significant P-values (after false discovery rate correction; threshold: $P = 0.0273$) are shown in bold.

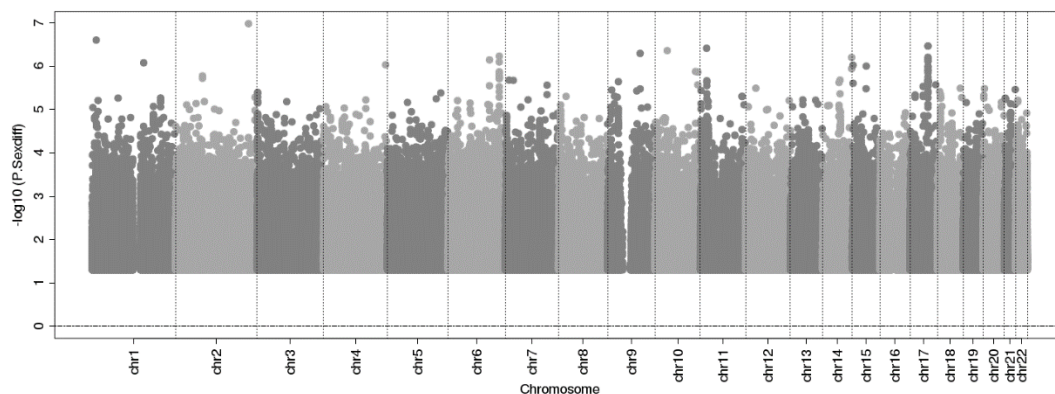
(See Supplementary Tables at the following URL:

<http://www.nature.com/mp/journal/vaop/ncurrent/supinfo/mp20175s1.html?url=/mp/journal/vaop/ncurrent/full/mp20175a.html>)

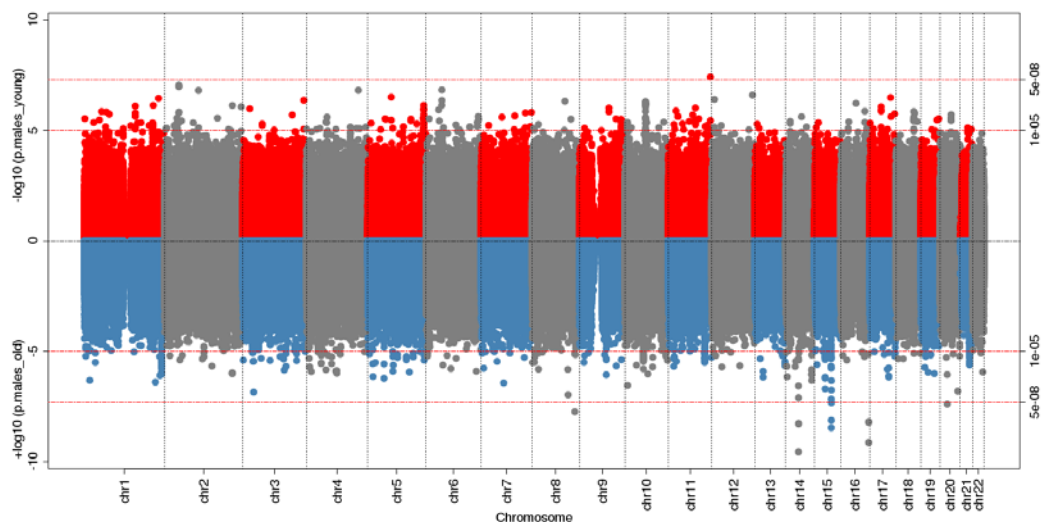
Supplementary Figure 5. A) Mani of P-values of the SNP-based association analysis of tiredness (responses to the question, “Over the past two weeks, how often have you felt tired or had little energy?”). The red line indicates the threshold for genome-wide significance ($P < 5 \times 10^{-8}$) and the threshold for suggestive significance ($P < 1 \times 10^{-5}$), the upper half shows the results for females and the bottom half shows the results for males. (B) Q-Q plot; pink for females and blue for males.

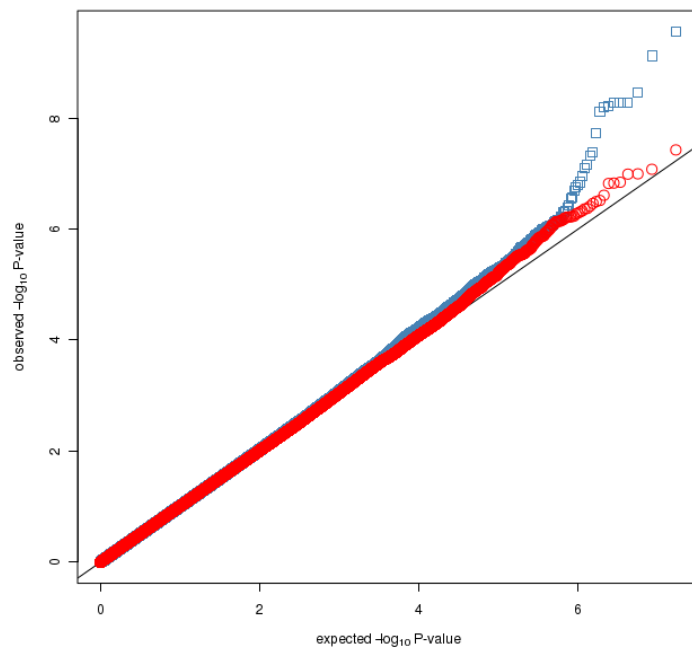


Supplementary Figure 6. Manhattan plot of the difference in effect size between males and females.

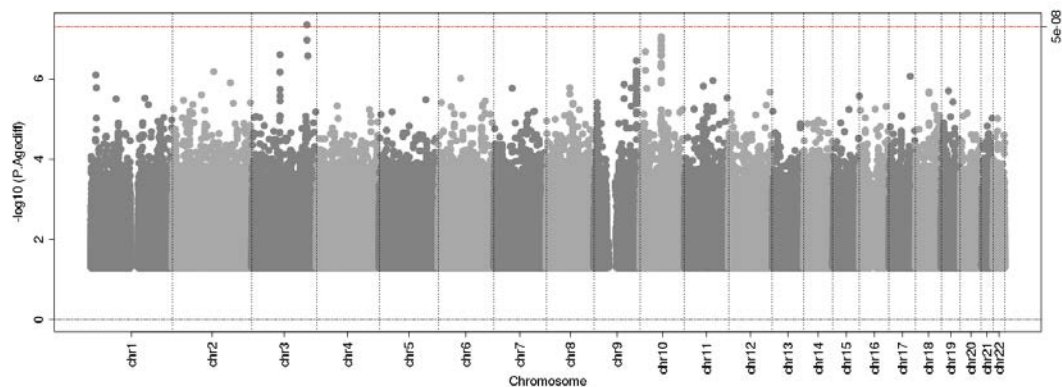


Supplementary Figure 7. A) Miami of P-values of the SNP-based association analysis of tiredness (responses to the question, “Over the past two weeks, how often have you felt tired or had little energy?”). The red line indicates the threshold for genome-wide significance ($P < 5 \times 10^{-8}$) and the threshold for suggestive significance ($P < 1 \times 10^{-5}$), the upper half shows the results for females and the bottom half shows the results for males. (B) Q-Q plot; red for males aged 40-50 years and blue for males aged 60-70 years.





Supplementary Figure 8. Manhattan plot of the difference in effect size between males aged 40-50 years and males aged 60-70 years.



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Appendix 6. List of publications

Hagenaars SP, Gale CR, Deary IJ, Harris SE. (in revision). Cognitive ability and health: a Mendelian randomization study. *Scientific Reports*.

Hagenaars SP, Cox SR, Hill WD, Davies G, Liewald DCM, CHARGE, McIntosh AM, Gale CR, Deary IJ. (under review). Genetic contributions to trail making test performance in UK Biobank. *Molecular Psychiatry*.

Hagenaars SP*, Hill WD*, Harris SE, Ritchie SJ, Davies G, Liewald D, Gale C, Porteous DJ, Deary I, Marioni R. (2017) Genetic Prediction of Male Pattern Baldness. *PLOS Genetics*. doi: 10.1371/journal.pgen.1006594

Deary V*, Hagenaars SP*, Harris SE, Hill WD, Davies G, Liewald DC, McIntosh AM, Gale CR, Deary IJ, International Consortium for Blood Pressure GWAS. (2017) Genetic contributions to self-reported tiredness. *Molecular Psychiatry*. doi: 10.1038/mp.2017.5

Reus LM, 7 authors, Hagenaars SP, 3 authors, McIntosh AM. (2017). Association of polygenic risk for major psychiatric illness with subcortical volumes and white matter integrity in UK Biobank. *Scientific Reports*. doi:10.1038/srep42140

Guadalupe T, et al, Hagenaars SP, et al, & Francks C (2016). Human subcortical brain asymmetries in 15,847 people worldwide reveal effects of age and sex. *Brain imaging and behaviour*. doi: 10.1007/s11682-016-9629-z.

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Hill WD*, Hagenaars SP*, Marioni RE, Harris SE, Liewald DC, Davies G, International Consortium for Blood Pressure, McIntosh AM, Gale CR, Deary IJ (2016). Molecular genetic contributions to social deprivation and household income in UK Biobank (n= 112,151). *Current Biology*. doi: 10.1016/j.cub.2016.09.035

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Weiss A, 8 authors, Hagenaars SP, 35 authors, Luciano M (2016) Personality Polygenes, Positive Affect, and Life Satisfaction. *Twin Research and Human Genetics* doi: 10.1017/thg.2016.65.

McIntosh AM, 5 authors, Hagenaars SP, 15 authors, Hocking LJ (2016) Genetic and Environmental Risk for Chronic Pain and the Contribution of Risk Variants for Major Depressive Disorder: A Family-Based Mixed-Model Analysis. *PLOS Medicine* doi: 10.1371/journal.pmed.1002090.

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